University of Alberta

The Efficacy of N-Acetylcysteine and Hydration Versus Placebo and Hydration In Decreasing Contrast-Induced Renal Dysfunction In Patients Undergoing Coronary Angiography With or Without Concomitant Percutaneous Coronary Intervention

By

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Abstract

A prospective, double-blind, randomized, placebo, controlled study was completed to assess the efficacy of N-Acetylcysteine in decreasing the incidence of contrast-induced renal dysfunction (CIRD) in patients with an acute coronary syndrome and renal insufficiency undergoing coronary angiography. With similar intravenous hydration protocols, 20 patients received N-Acetylcysteine (Treatment Group) and 20 patients received placebo (Control Group). The Treatment and Control Groups were similar at baseline on demographic, clinical characteristics, and pre-existing renal insufficiency. CIRD, occurred in 7.5% of the cohort, with 2.5% in the Treatment Group, and 5.0 % in the Control Group, for an absolute difference of 2.5%. There were no differences in creatinine from baseline, to 24 hours, or to 48 hours between the Treatment and Control Groups. Similarly, there were no significant differences in creatinine clearance to 24 hours, or to 48 hours. These results suggest that this cohort gained no added protection to renal function with the use of N-Acetylcysteine.

Frontispiece

We see the universe the way it is because if it were different we would not be here to observe it – be humbled by it. The energy, which makes up the universe cannot be created out of nothing and is constantly changing forms, moving towards chaos – expect it. In everything that we do there is always a positive energy and a negative energy, the one with negative energy is condemned to be short-lived – be filled and inspired by the positive. The increase in entropy with time gives direction to time, distinguishing the past from the future – cherish the past and dream of the future. There is no absolute time, but instead ones own personal measure of time that depends on where one is and how one is moving – never worry about time, it takes care of itself. Be true to you and live in and for the moment. – R. A. Seyon, March, 2004.

Inspired by the writings of Stephen Hawking, (1996). *A brief history of time: The updated and expanded tenth anniversary edition*. New York: Bantam Books.

Dedication

To Mommy and Daddy and Manju,

I am, because of all that you are;

Forever will you nurture, guide, support and, protect me.

To the One who has inspired me;

Anand, forever will you bring out the best in me.

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The completion of this thesis marks a fork in the path, which I have walked along for sometime. These pages seem to dwarf in significance compared to the individual whom I have become through the journey on this path; a journey I could have never imagined would have been filled with so many lessons and experiences. I have been educated, not only through academia, but also on many other levels, and in many different ways; each of them molding me into the woman I have become. And to each of you whose paths I have crossed and walked a distance with, forever will I cherish the memories and forever my undying gratitude for all that you brought to my life during our journey together. My Daddy always says education, whatever the form, is a discipline. I stand now, at the end of this path, a little more disciplined, humbled, and poised for the next path I embark on. I pray that its journey may be as enlightening, liberating, and humbling.

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CHAPTER ONE

Introduction

Although there has been a decline in cardiovascular disease (CVD), which includes ischemic heart disease (IHD), acute myocardial infarction (AMI), cerebrovascular disease, and other cardiovascular diseases, it remains one of the most prevalent medical conditions in North America. Furthermore, although hospitalizations for CVD as a whole, which includes IHD, AMI, and congestive heart failure (CHF), have been declining since 1985, it still remains the leading cause of hospital admissions, accounting for 18% for all hospital admissions (Heart and Stroke Foundation of Canada [HSFC], 2003). There are about 12.5 million Americans with coronary heart disease (CHD), with the average age of a person having their first attack is 65.8 years for men and 70.4 years for women (American Heart Association [AHA], 2001). Reported to be the leading cause of death, CVD accounts for nearly 40% of the total number of deaths in both Canada and the United States (AHA, 2001; HSFC, 1999).

Between 1991 and 2001, the Canadian population aged 80 years and over rose 41% and is expected to increase an additional 43% over the next 10 years. As the baby-boomers enter into the middle-aged group, seniors, over the age of 65 years, constitute close to 14% of the Canadian population as of 2001. It is at the age of 60 years where hospital admission rates begin to increase for IHD and CHF, with ages 80 years to 89 years constituting the largest group (HSFC, 2003). In this age group these forms of heart disease can be primarily attributed to CHD (AHA, 2001; Benitez & Vogel, 2001; Cotran, Kumar, & Collins, 1999), which is likely to be associated with other co-morbidities such as smoking, hypertension, dyslipidemia, and diabetes mellitus (Kannel, 2000).

For patients who present with acute coronary syndromes, which encompasses IHD and AMI, risk stratification with noninvasive or invasive testing is done to obtain valuable information about the disease state to assist in deciding upon an appropriate treatment regimen. Amongst the various methods of risk stratification, coronary angiography has become an increasingly utilized method of investigation (AHA, 2001; Scanlon et al., 1999). Coronary angiography falls under the domain of interventional cardiology, and provides radiographic visualization of the coronary arteries and cardiac chambers. The procedure and contrast media used in coronary angiography has associated risks of death, arrhythmias, myocardial infarction, cerebrovascular accident, vascular complications, hemodynamic complications, perforation of cardiac chambers and vessels, contrast reactions, and contrast-induced renal dysfunction (CIRD) (Scanlon et al., 1999).

The kidneys require a plentiful supply of blood with an adequate perfusion pressure to maintain their complex level of functioning; and are therefore, dependent on an adequate cardiac output, of which approximately 25% is received by the kidneys (Cotran et al., 1999). In the face of an AMI the ability of the heart to generate an adequate cardiac output and perfusion pressure is hindered due to necrosis, stunning, and hibernation of the myocardium (Baer & Erdmann, 1998). In patients without pre-existing renal insufficiency the risk of developing a significant reduction in renal function is 0% to 0.5% (Scanlon et al., 1999). The incidence of CIRD has been shown to range anywhere from 10% to 40% following coronary angiography in patients with pre-existing renal insufficiency (Scanlon et al., 1999; Spinler & Goldfarb, 1992). The risk of renal dysfunction is increased with the presence of other disease states that alter or impair renal function, for example diabetes mellitus and hypertension (AHA, 2001; Deray & Jacobs, 1995; Morcos, Thomsen, Webb, & Members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology, 1999; Quader, Sawmiller, & Sumpio, 1998; Scanlon, et al., 1999; Spinler & Goldfarb, 1992; Tommaso, 1994). Many of these co-morbidities may be present in the population that presents with an acute coronary syndrome.

The toxic effects of contrast media have been recognized for over half a century. Many studies have looked at the use of different treatment modalities to reduce the incidence or level of renal impairment incurred with the use of contrast media in systemic and coronary angiography including hydration, furosemide, dopamine, mannitol, calcium channel blockers, and atrial natriuretic peptide, as well as low and high osmolar contrast agents (Abizaid et al., 1999; Davidson et al., 1989; Martin-Paredero et al., 1983; McCullough, Wolyn, Rocher, Levin, & O'Neill, 1997; Parfrey et al., 1989; Schwab et al., 1989; Solomon, Werner, Mann, D'Elia, & Silva, 1994; Stevens et al., 1999; Taliercio et al., 1991; Tepel, Van Der Giet, Schwarzfeld, Laufer, Liermann, & Zidek, 2000). No form of treatment or modification of technique in imaging has been shown to be efficacious in decreasing the incidence of CIRD.

Tepel et al. (2000) were the first investigators to assess the benefit of prophylactic oral administration of N-Acetylcysteine with intravenous hydration in reducing CIRD secondary to the administration of a nonionic, low osmolality contrast agent, iopromide, in patients with chronic renal insufficiency, many of whom underwent computed tomography for investigation of abdominal and thoracic illnesses. Subsequently, there have been several studies, which have investigated the efficacy of N-Acetylcysteine in the patient who undergoes coronary angiography with or without concomitant percutaneous coronary intervention in decreasing the incidence of CIRD. The results of these investigations warrant further investigation to determine the efficacy of N-Acetylcysteine in the patient who presents with an acute coronary syndrome in reducing the incidence of CIRD.

As medical therapies improve, more and more patients with renal insufficiency and multiple co-morbidities will present with an acute coronary syndrome, specifically AMIs, and require risk stratification using coronary angiography. Patients who suffer an AMI (non-ST elevation myocardial infarction or ST elevation myocardial infarction) have the added risk factor of suboptimal heart functioning which can predispose them to CIRD (AHA, 2001; Davidson et al., 1989; Deray & Jacobs, 1995; Morcos et al., 1999; Scanlon et al., 1999; Spinler & Goldfarb, 1992; Taliercio, McCallister, Holmes, Ilstrup, & Vlietstra, 1989; Tommaso, 1994). In reviewing the literature, there has been no treatment modality identified which has been shown to be efficacious in reducing the incidence or level of renal dysfunction incurred with the use of contrast media in coronary angiography. The only incomplete protective modality in safeguarding patients from CIRD is hydration (Murphy, Barrett, & Parfrey, 2000). However, many patients who suffer an acute coronary syndrome, specifically a non-ST elevation myocardial infarction or ST elevation myocardial infarction, are placed on diuretic therapy to manage clinical signs of failure (i.e., pulmonary edema or increased jugular venous pressure) and are consequently not given additional intravascular volume.

The most promising treatment modality to date has been with the use of N-Acetylcysteine and hydration. The use of N-Acetylcysteine has been welcomed into many practices as a prophylactic therapy against CIRD. However, no protocols or guidelines have been developed or introduced by any recognized association for the implementation of this prophylactic therapy. Currently, the standard of care in the management of patients with renal insufficiency who require coronary angiography is minimization of the volume of contrast agent, careful utilization of nephrotoxic drugs, and prehydration.

To date, several studies have been conducted to investigate the efficacy of N-Acetylcysteine. In reviewing these studies they varied in cohort, type of angiographic testing, degree of renal insufficiency, and intervention protocols in comparison to the original study by Tepel et al. (2000), which makes comparing and critiquing these studies difficult to determine the actual benefit of N-Acetylcysteine. The absolute difference in the incidence of CIRD varied from 37% to –3% in favour of the use of N-Acetylcysteine. These results also reflect the use of N-Acetylcysteine in cohorts other than those patients who present with an acute coronary event. The efficacy of N-Acetylcysteine and hydration in patients who present with an acute coronary syndrome and have pre-existing renal insufficiency therefore requires further clinical investigation.

Purpose of the Study

The purpose of this study was to examine the efficacy of N-Acetylcysteine and hydration in decreasing the incidence of CIRD in patients who presented with an acute coronary syndrome to the Royal Alexandra Hospital. The hypothesis of this study was that the administration of N-Acetylcysteine and intravenous hydration would decrease the incidence of CIRD, as defined as an absolute increase in serum creatinine of greater than

44 µmol/L and/or a relative increase of 25% above baseline within 48 hours of contrast media exposure. The hypotheses tested were:

1. Patients administered oral N-Acetylcysteine and intravenous hydration would have a lower incidence of CIRD than patients administered placebo and intravenous hydration.
2. Patients administered oral N-Acetylcysteine and intravenous hydration would have an attenuation in change of serum creatinine than patients administered placebo and intravenous hydration.
3. Patients administered oral N-Acetylcysteine and intravenous hydration would maintain or improve the level of creatinine clearance than patients administered placebo and intravenous hydration.

Significance of Study

The high incidence of CIRD places added risks to patients during their hospital stay, as well as added costs to the health care system. The search for a treatment modality to decrease the incidence of CIRD has not yet yielded a proven therapy. The introduction of N-Acetylcysteine has been welcomed into many practices as a prophylactic therapy to decrease the incidence of CIRD. However, there are no data to date to support the use of this treatment modality in the patient who presents with an acute coronary syndrome. The purpose of this study was to examine the efficacy of N-Acetylcysteine and intravenous hydration in decreasing the incidence of CIRD in those patients who presented with an acute coronary syndrome and renal insufficiency to generate evidence to support the use of N-Acetylcysteine in this cohort. The data generated may then be utilized to develop and support a protocol that would ensure that patients are appropriately screened and treated for the prophylactic prevention of CIRD when undergoing coronary angiography.

CHAPTER TWO

Literature Review

A search of the literature was conducted to quantify the incidence and clarify the definition of contrast-induced renal dysfunction (CIRD); and to explore the theorized mechanisms and determine the identified risk factors for the development of CIRD. The search also was done to investigate and review the therapies for the prevention of renal dysfunction in patients who undergo coronary angiography. The computer online search engines and resources used included the National Library of Medicine – Pubmed, Medline, and Gateway; as well as HKN, CINAHL, OVID, and GOOGLE. The search was limited to studies that included patients undergoing coronary angiography and coronary angioplasty. The keywords used included, N-Acetylcysteine, mucomyst, parvolex, CIRD, contrast-induced nephropathy, contrast-induced renal failure, contrast-induced renal insufficiency, contrast-induced renal impairment, contrast media, contrast agent, and complications of angiography. In addition to these search strategies, the expertise of the medical library technicians at the Royal Alexandra Hospital were also called upon to ensure an exhaustive and complete search was achieved and articles retrieved.

Incidence of Contrast-Induced Renal Dysfunction

The complication rate of coronary angiography has been investigated since the early 1970s (Adams, Fraser, & Abrams, 1973; Bourassa & Noble, 1976; Davis, Kennedy, Kemp, Judkins, Gosselin, & Killip, 1979). These earlier studies primarily determined the incidence of death, procedure-related acute myocardial infarction, ventricular fibrillation, and prolonged arrhythmias, embolization, and vascular complications (i.e., thrombosis, hemorrhage, and pseudoaneurysm). One of the first investigations to review the incidence of CIRD in coronary angiography was done by Weinrauch et al. (1977). The population had known diabetes mellitus-Type I and azotemic diabetic nephropathy and were undergoing coronary angiography as part of the work-up for renal transplantation. Twelve of the 13 patients developed some evidence of acute renal failure, as defined as a mean increase in serum creatinine of 365.2 μmol/L, mean increase in serum potassium of 0.8 mEq/L, and a mean decrease in urine volume of 850 ml/day.

Subsequently, CIRD has been reported as the third leading cause of new onset renal dysfunction in hospitalized patients (McCullough, Wolyn, Rocher, Levin, & O'Neill, 1997; Tommaso, 1994). Davidson et al. (1989) found that serum creatinine levels, on average, increased 11.5 μmol/L at 24 hours and 16.8 μmol/L at 48 hours, from a baseline creatinine of 90.2 μmol/L. These observations suggest that all patients who receive a contrast agent have a measurable loss of renal function, despite normal renal function prior to contrast administration. CIRD has been the subject of numerous investigations for a method to safeguard the kidneys from the often transient toxic effects of contrast agents. The incidence of CIRD in the general population undergoing diagnostic imaging with the use of a contrast agent ranges from 0.1% to 13%, with the variability largely due to the lack of a consistent definition of CIRD (Quader, Sawmiller, & Sumpio, 1998). In patients undergoing coronary angiography with renal insufficiency, the incidence of worsening renal function ranges from 10% to 40% (Scanlon et al., 1999; Spinler & Goldfarb, 1992). In patients undergoing the same procedure without evidence of pre-existing renal insufficiency, the risk of developing a significant reduction in renal function is 0% to 0.5% (Scanlon et al., 1999).

In 1986, Taliercio, Vlietstra, Fisher, and Burnett identified that patients with pre-existing renal dysfunction (a serum creatinine level of 176.8 μmol/L or greater) undergoing coronary angiography had an incidence rate of 23% for an increase in serum creatinine by 88.4 μmol/L or greater. They found the existence of New York Heart Association (NYHA) Class IV heart failure, multiple radiocontrast studies within 72 hours, dose of contrast agent, and diabetes mellitus requiring insulin therapy were independently associated with CIRD. In the patients without these risk factors the incidence of CIRD was 2%. Rich and Crecelius (1990) focused on patients greater than 70 years of age and found that 11% had a serum creatinine rise of greater than 44 μmol/L above baseline. The independent risk factors for this elderly group were identified as a contrast volume greater than 200 ml, a serum albumin level less than 35 g/L, presence of diabetes mellitus, a serum sodium level less than 135 mmol/L, and a baseline creatinine greater than 133 μmol/L. Rich and Crecelius found the incidence of CIRD varied from 1.2% in patients with no risk factors to more than 20% in those that had two or more risk factors.

In a more recent retrospective study of acute renal failure after coronary intervention, McCullough et al. (1997) found that the overall incidence was 144.6/1000 with 7.7/1000 requiring dialysis. McCullough et al. stated that the overall incidence of CIRD in these 1826 consecutive patients undergoing coronary intervention was 14.5%, which was similar with findings from other studies (Cochran, Wong, & Roe, 1983; Gomes et al., 1985; Martin-Paredero et al., 1983; Rich & Crecelius, 1990; Spinler & Goldfarb, 1992; Taliercio et al., 1986). In a Heartwire publication released on March 17, 2002 (www.theheart.org), researchers at the Lenox Hill Heart and Vascular Institute found that the incidence rate of CIRD in 8268 consecutive patients undergoing percutaneous coronary intervention was 16.5%. A multivariate analysis showed that baseline chronic renal failure, diabetes mellitus, female gender, age, and severe heart failure were all independent predictors of CIRD.

There are several difficulties in evaluating the incidence of CIRD. In addition to the many terminologies, one of the difficulties is the varying definitions used to describe the response of the kidneys following contrast exposure. The definition of CIRD varies from study to study, as does the markers used to evaluate renal function. Some studies define CIRD as an elevation of 0.5 mg% or 1.0 mg% of serum creatinine over the baseline value (Kapoor et al., 1996), whereas other studies use a 25% or 50% rise over baseline creatinine (Abizaid et al., 1999; Briguori et al., 2002; Diaz-Sandoval, Kosowsky, & Losordo, 2002; Murphy et al., 2000; Parfrey et al., 1989; Spinler & Goldfarb, 1992; Tepel, Van der Giet, Schwarzfeld, Laufer, Liermann, & Zidek, 2000). Other studies use a common definition of an increase in serum creatinine of 44 μmol/L to 88 μmol/L (Solomon, Werner, Mann, D'Elia, & Silva, 1994; Spinler & Goldfarb, 1992; Tepel et al., 2000). Some studies have also placed a timeline for serum creatinine levels to rise, varying most often from 24 hours to 72 hours (Solomon et al., 1994; Spinler & Goldfarb, 1992; Taylor, Hotchkiss, Morse, & McCabe, 1998; Tepel et al., 2000). In a consensus report on CIRD, published in 1999, Morcos, Thomsen, Webb, and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology defined CIRD as "an impairment of renal function (an increase in serum creatinine by more than 25% or 44 μmol/L [occurring] within three days following the intravascular administration of a contrast medium in the absence of an alternative etiology" (p. 1611).

Other markers used to evaluate renal function have been glomerular filtration rate and concentration of kidney tubular cell enzymes in urine, but the latter has not been clearly clinically correlated (Spinler & Goldfarb, 1992).

As a result of the varying definitions and the ambiguity of what is considered renal impairment the serum biochemical marker of renal dysfunction as entry criteria into studies vary. In some studies the serum creatinine is 106.8 μmol/L, while in others it is 123.8 μmol/L, and in others it is 176.8 μmol/L. Another criteria used in studies is the calculated creatinine clearance with less than 30 ml/min to less than 60 ml/min defining renal impairment. Still other studies use a combination of both serum creatinine and creatinine clearance. Due to the varying definitions of renal impairment and different populations, the comparison of results of one study to another is difficult.

Another difficulty arises from the various types of design studies used for investigation. Retrospective studies may underestimate the incidence of CIRD because of the absence of comparable laboratory data prior to and following contrast administration. The prospective study estimates may vary based on different patient populations (i.e., primary cardiac versus noncardiac diagnosis); the degree of follow-up (e.g., 24-hour versus 48-hour versus 72-hour serum creatinine measurements); and other uncontrolled variables (e.g., level of hydration, and amount and type of contrast agent administrated). As a result of these inconsistencies from one study to another it is difficult to compare and evaluate the findings between studies.

Mechanism of Contrast-Induced Renal Dysfunction

The exact etiology of CIRD has not been established, but there are several theorized mechanisms. The first and most commonly associated mechanism is an interference with renal perfusion caused by the injection of contrast media with high osmolality. Initially, there is a transient vasodilation and increase in renal blood flow followed by vasoconstriction and a reduction in renal blood flow, which is proportional to the osmolality of the injected substance. Most animal studies have shown that following contrast media exposure there is a decrease in renal blood flow and glomerular filtration rate secondary to the vasoconstriction effects. These effects appear to be more pronounced in states of dehydration when investigated in animal models. The vasoconstriction that is seen is thought to be partly hormonally mediated. Increased levels of endothelin and decreased levels of prostaglandins and nitric oxide subsequent to the nonionic contrast media effects on the endothelium, which potentiate the vasoconstricting effects seen following contrast exposure, have been observed in laboratory studies (Nikolsky & Mehran, 2003). The net effect of this alteration in renal perfusion is renal ischemia (Deray & Jacobs, 1995; Spinler & Goldfarb, 1992; Tommaso, 1994).

A second theorized mechanism is a transient increase in glomerular permeability to filter proteins. The filtration of proteins and enzymes could lead to tubular injury after such a protein flow, but correlative histologic evidence has not been demonstrated (Deray & Jacobs, 1995; Spinler & Goldfarb, 1992; Tommaso, 1994). Direct tubular injury and intraluminal obstruction from renal exposure to contrast media or the crystallization of contrast with uric acid, protein, or oxalate, respectively, have also been suggested etiologies (Deray & Jacobs, 1995; Spinler & Goldfarb, 1992; Tommaso, 1994). The direct toxic effects of contrast media were studied using a canine model. Contrast media were shown to reduce the transepithelial resistance, inulin permeability, polarized cellular enzyme release and other parameters of renal tubular cell viability. The resultant renal tubule cell injury causes a series of changes, including increased tubule calcium ion content and decreased tubule potassium, adenosine triphosphate, and uncoupled respiratory rates. Because of the altered cellular metabolism oxygen free radicals overwhelm the mitochondria and result in a cytotoxic effect to the kidneys. Contrast agents also have been found to decrease the activity of antioxidant enzymes catalase and superoxide dismutase compounding the cytotoxic effects of oxygen free radicals. Another proposed mechanism for cell injury is apoptosis secondary to the hyperosmolality of the ionic and first generation nonionic contrast agents. It was thought that N-Acetylcysteine would be able to decrease the oxidative stress, which trigger apoptosis, but laboratory trials failed to show this (Nikolsky & Mehran, 2003).

The last proposed mechanism is a hypersensitivity reaction to contrast and is based on an immunologically mediated response causing interstitial nephritis. Studies involved in investigating this proposed mechanism are looking at the effects of contrast media on the complement system, specifically C5 and C3, but no conclusive results have been found to date (Nikolsky & Mehran, 2003). This is a very rare phenomenon and not thought to be the predominant mechanism for CIRD (Deray & Jacobs, 1995; Tommaso, 1994).

Risk Factors for Contrast-Induced Renal Dysfunction

The use of radio-opaque agents to define the structure and pattern of blood vessels began in 1896, when a combination of bismuth, lead, and barium salts was injected into an amputated arm (Quader et al., 1998). In 1927, Moniz was the first to use a contrast agent composed of sodium iodide in live humans to perform a carotid angiography. The toxic effects of this agent were apparent immediately due to the pain, parasthesia, paresis, and thrombosis that occurred after injection. Over subsequent decades structural modifications have been made to decrease the toxic effects incurred by contrast agents.

The largest advancement made in the structural modification of contrast agents was the introduction of the first nonionic and low osmolality contrast agent, mitrezamide, in the 1970's (Quader et al., 1998; Sullivan, Wainwright, Reidy, & Sowton, 1984). Since its introduction in 1972, the nonionic and low osmolality contrast agents have been compared to ionic and high osmolality agents to determine the safety and effects during and following angiography on cardiac function (i.e., angina, asystole, bradycardia, hypotension, hypertension, ventricular tachycardia/fibrillation, pulmonary edema, and acute myocardial infarction). Iohexol compared to diatrizoate, repeatedly, showed a lower incidence of adverse cardiac reactions (Bettmann & Higgins, 1985; Bettmann, Bourdillon, Barry, Brush, & Levin, 1984; Matthai, Kussmaul, Krol, Goin, Schwartz, & Hirshfeld, 1994; Sullivan et al., 1984). One particular study by Hill et al. (1993) demonstrated that iohexol versus diatrizoate contrast media related adverse outcomes were 10.2% versus 31.6%, respectively ($p < 0.001$); and cardiac adverse events were 7.2% versus 24.5%, respectively ($p < 0.001$). In comparing ionic versus nonionic contrast agents with the incidence of CIRD following cardiac catheterization the investigations reviewed in this literature search did not demonstrate a statistically significant difference (Davidson et al., 1989; Katholi et al., 1993; Rudnick et al., 1995; Schwab et al., 1989; Taliercio et al., 1991).

The American College of Cardiology put forth a position statement on the use of low osmolar agents stating that these agents produced less adverse electrophysiologic and hemodynamic alterations, reduced the risk of provoking myocardial ischemia, and caused less subjective sensation of discomfort for the patient (Ritchie et al., 1993). At the time the American College of Cardiology was uncertain of the clinical evidence for CIRD because of the small difference in nephrotoxicity occurring in those patients who received low osmolality, nonionic agents compared to those who received high osmolality ionic agents. As a result the College came out with a position statement that indicated because of the small difference in nephrotoxicity seen between the two agents there was no substantial evidence to make the use of low osmolality nonionic agents an absolute indication. Recently, Murphy et al. (2000) stated that based on accumulated evidence to date the use of nonionic, low osmolality should be considered for patients with renal insufficiency secondary to diabetes mellitus. Despite all the attention that has been given to this frequent complication following coronary angiography, strategy suggestions have not been incorporated into guidelines to reflect current evidence.

Additionally, the risk of renal dysfunction following exposure to contrast media is increased with the presence of pre-existing renal insufficiency, diabetes mellitus, heart failure, volume depletion, dehydration, previous diuretic usage, concomitant exposure to nephrotoxic drugs, increased age, multiple myeloma, dose of contrast, type of contrast (nonionic versus ionic), repeated exposure to contrast media used in diagnostic investigations, and injection site (intra-arterial versus intravenous) (AHA, 2001; Davidson et al., 1989; Deray & Jacobs, 1995; Morcos et al., 1999; Scanlon et al., 1999; Spinler & Goldfarb, 1992; Taliercio et al., 1989; Tommaso, 1994). Other risk factors that have been postulated, but not confirmed include hypotension, hypertension, renal ischemia, anemia, proteinuria, hyponatremia, abnormal liver function, hypoalbuminemia, hyperuricemia, peripheral vascular disease, and renal transplantation (AHA, 2001; Davidson et al., 1989; Deray & Jacobs, 1995; Morcos et al., 1999; Scanlon et al., 1999; Spinler & Goldfarb, 1992; Taliercio et al., 1989; Tommaso, 1994). Renal insufficiency has been identified as an independent risk factor (Deray & Jacobs, 1995; Scanlon et al., 1999; Spinler & Goldfarb, 1992).

Prophylactic Therapies to Decrease the Incidence of Contrast-Induced Renal Dysfunction

Hydration and Contrast-Induced Renal Dysfunction

Weinrauch et al. (1977) studied 13 high risk patients with a mean age of 33 years for acute renal failure, who had known diabetes mellitus-Type I, hypertension, azotemia, anemia, a mean serum creatinine of 601.1 µmol/L, required potent diuretics, and were undergoing prospective coronary angiography as part of the work-up for renal transplantation. They were not placed on a fluid restriction for more than 12 hours, were not hypotensive or dehydrated prior to the procedure, and were not receiving nephrotoxic drugs concurrently. They received 100 ml to 300 ml of iodinated contrast material (methylglucamine diatrizoate, 66%, sodium diatrizoate, 10%). Twelve of the 13 patients developed acute renal failure with a mean increase in serum creatinine of 344.8 µmol/L that ranged from 106.1 µmol/L to 574.6 µmol/L. This was the first study demonstrating that congestive heart failure was not a necessary component for the development of acute renal failure. All patients who received greater than 65 ml/m^2 of iodinated contrast developed acute renal failure. As well, it was observed that no patients with a hemoglobin of greater than 9.9 g/dl required dialysis or potassium exchange resin.

In another prospective study, 220 consecutive patients were observed for nephrotoxicity following radiographic procedures requiring injection of a contrast medium by Parfrey et al. (1989). There were three study groups who received contrast media: (a) patients with diabetes mellitus and normal renal function (n = 85), (b) patients with pre-existing renal insufficiency (serum creatinine above 150 μmol/L) without diabetes mellitus (n = 101), and (c) patients with both pre-existing renal insufficiency and diabetes mellitus (n = 34). The control group (n = 268) had diabetes mellitus, pre-existing renal insufficiency, or both, but did not receive any contrast material for computed tomography scanning or abdominal imaging. The proportion of the insulin-dependent diabetic patients was higher in the control group. The contrast group had a significantly higher mean (± SD) blood pressure value, (138 ± 22 mmHg/81 ± 12 mmHg versus 131 ± 23 mmHg/77 ± 13 mmHg, contrast group versus control group, respectively), and a greater proportion of patients with chronic renal failure, (88% versus 78%, in the contrast group versus in the control group, respectively). The mean (± SD) volume of contrast agent used was 122 ± 90 ml, and the majority received intravenous contrast material or underwent coronary angiography. Patient's physicians were advised to prescribe 0.45% normal saline intravenously for two days following imaging at a rate equal to urine output. There was no implementation of any other prophylactic measures. Clinically significant acute renal failure (defined as an increase in serum creatinine level above 50% two days following procedure) occurred only in those patients with both diabetes mellitus and pre-existing renal insufficiency at a rate of 8.8% in the contrast group compared to 1.6% in the control group. Acute renal insufficiency, relatively defined as an increase of greater than 25% in serum creatinine, was seen in 7.0% of all patients who had pre-existing renal insufficiency, compared to 1.5% in the control group. The cause of the acute renal insufficiency was attributed to the contrast material. The risk of acute renal insufficiency attributable to the contrast material was therefore 5.5%, and the relative risk associated with the infusion of contrast material was 4.7%. These rates were similar regardless of whether the osmolality of the agent was high or low.

In 1990, Manske, Sprafka, Strony, and Wang investigated 59 insulin-dependent diabetics undergoing coronary angiography with the use of nonionic agents who were being evaluated for renal transplantation for acute renal failure. This cohort had a mean serum creatinine of 521.6 µmol/L and a urine creatinine clearance of less than 30 ml/min. Patients were excluded if they were initiated on an angiotensin converting enzyme inhibitor within one week of the study, undergoing dialysis, or underwent coronary artery bypass graft surgery within three days of the study. The historical control group of 21 insulin-dependent diabetic patients was formed using patients from the previous two years when coronary angiography was not a routine part of the work-up for renal transplantation. The mean serum creatinine, creatinine clearance, and mean arterial pressure were similar between both groups. More patients in the investigation group were taking angiotensin converting enzyme inhibitors, calcium channel blockers, and furosemide than in the control group. All patients received a prehydration protocol of 150 ml/hr of intravenous 5% dextrose in 0.45% normal saline with 25 g of mannitol two hours prior to the procedure. Contrast nephropathy, defined as a serum creatinine increase of greater than 25% when measured 48 hours after radiocontrast exposure, occurred in 50% of the intervention group and none in the control group. There was a significant association with dye quantity (odds ratio = 10.6; 95% confidence interval 2.08 to 60.6), ejection fraction of or less than 50% (odds ratio = 10.0; 95% confidence interval

1.0 to 69.4), and low arterial pressure (odds ratio = 12.3; 95% confidence interval 1.26 to 81.6) as risk factors for contrast nephropathy.

To validate an outpatient protocol for hydration Taylor et al. (1998) randomized 36 patients undergoing elective cardiac catheterization with renal dysfunction (serum creatinine of or greater than 123.8 µmol/L, and creatinine clearance between 25 ml/min to 60 ml/min) to receive either one of two protocols. The first protocol involved overnight intravenous hydration with 0.45% normal saline at 75 ml/hr for both 12 hours before and following cardiac catheterization. The second was an outpatient hydration protocol of 1000 ml of clear fluids to be taken orally over 10 hours followed by six hours of intravenous hydration of similar crystalloid at 300 ml/hr initiated 30 minutes to 60 minutes prior to catheterization. The exclusion criteria for this study included known or suspected cardiomyopathy with an ejection fraction less than 30%, clinical evidence of pulmonary edema (i.e., increased jugular venous distension, pulmonary rales, and/or S3 gallop), known or suspected valvular disease, or ongoing myocardial ischemia. The serum creatinine was measured at 12 hours and 24 hours before cardiac catheterization; and at 24 hours and 48 hours after cardiac catheterization.

The patients' mean (± SD) age was 70 ± 8 years; with 29 of the 36 being males. The inpatient and outpatient groups were well matched with respect to age, cardiovascular diagnosis, angiotensin converting enzyme inhibitors usage, diabetes mellitus, and baseline renal function, (serum creatinine [M ± SD] 153.8 ± 38.9 µmol/L and 154.7 ± 30.9 µmol/L for inpatients and outpatients, respectively). The maximal change in creatinine (M ± SD), the primary endpoint, was not significant at 18.6 ± 33.6 µmol/L and 10.6 ± 20.3 µmol/L in the inpatient and outpatient groups, respectively. The secondary endpoints, the change in creatinine (M ± SD) at 24 hours (7.1 ± 22.1 µmol/L and –0.9 ± 23.9 µmol/L, in the inpatient and outpatient groups, respectively), and at 48 hours (11.5 ± 38.9 µmol/L and 6.2 ± 19.5 µmol/L, in the inpatient and outpatient groups, respectively) were also not significantly different between the groups. Three patients, one in the outpatient group and two in the inpatient group, met the criteria for contrast-associated nephropathy, which was defined as an increase in creatinine of or above 44.2 µmol/L.

Recently, through a prospective, randomized, controlled, open-label trial, Mueller et al. (2002) investigated 1620 patients who were scheduled for elective or emergency coronary angioplasty. This group of investigators studied the effects of different isotonic solutions in the prevention of contrast media-associated nephropathy. Patients who presented and agreed to participate in the study were intravenously administered 0.9% normal saline or 5% dextrose in 0.45% normal saline at a rate of 1 ml/kg/hr for a 24-hour period on the day of contrast media exposure. For patients who presented for emergency intervention, no protocol-defined prehydration could be given. In patients with an acute coronary syndrome and selected patients with stable coronary disease, angioplasty was preformed immediately after the diagnostic angiography; whereas percutaneous coronary intervention was scheduled 48 hours post diagnostic angiography if they had stable angina. Low osmolar nonionic contrast media was utilized, with no N-Acetylcysteine given or changes in medication dosages during the study period.

The demographic characteristics of the final 1383 patients included in this study were well balanced between the treatment groups with a mean age of 64 years. The baseline renal function was deemed as normal in most patients with a mean serum creatinine of 116.7 µmol/L, with a range from 110.5 µmol/L to 122.0 µmol/L, in the group receiving isotonic solution, and 115.8 µmol/L, with a range from 109.6 µmol/L to 121.1 µmol/L, in the group receiving half isotonic solution. Contrast media-associated nephropathy, defined as an increase in serum creatinine of at least 44.2 µmol/L within 48 hours, occurred in 5 versus 14 patients in the isotonic and half isotonic groups, respectively. The incidence of nephropathy was significantly reduced in the isotonic group (0.7% versus 2.0%, $p = 0.04$). The three groups benefiting the most from the isotonic prehydration were: (a) women, (b) patients with diabetes, and (c) those receiving 250 ml or more of contrast media. The serum creatinine level change was small and only reported for the afore mentioned subgroups. The increase in serum creatinine ranged from 3.5 µmol/L to 10.6 µmol/L. At 48 hours serum creatinine was measured, and in women increased 3.5 µmol/L (95% confidence interval, 1.8 µmol/L to 6.2 µmol/L) in the isotonic group versus 8.8 µmol/L (95% confidence interval, 4.4 µmol/L to 13.3 µmol/L) in the half isotonic group ($p = 0.06$). Being female carried an odds ratio of 3.9, ($p = 0.05$), for the development of nephropathy. In the diabetic group serum creatinine increased 3.5 µmol/L (95% confidence interval, 8.8 µmol/L to 6.2 µmol/L) in the isotonic group versus 10.6 µmol/L (95% confidence interval, 4.4 µmol/L to 15.9 µmol/L) in the half isotonic group ($p = 0.04$). In patients receiving 250 ml or more of contrast material serum creatinine increased 4.4 µmol/L (95% confidence interval, 2.7 µmol/L to 6.2 µmol/L) in the isotonic group versus 7.1 µmol/L (95% confidence interval, 4.4 µmol/L to 9.7 µmol/L) in the half isotonic group ($p = 0.06$). The incidence of nephropathy also was higher in patients with creatinine levels above 141.4 µmol/L.

The evidence for hydration prior to contrast exposure has never been tested with a randomized, controlled trial of deliberate hydration versus no intervention for the prevention of CIRD (Murphy et al., 2000). The evidence for the use of hydration has been based on comparison with other treatment modalities, and it is evident that it does not provide complete protection from CIRD (Murphy et al., 2000; Solomon et al., 1994). The benefits of prehydration are thought to correct subclinical dehydration prior to contrast media exposure, while hydration following contrast media exposure counters an osmotic diuresis that occurs (Murphy et al., 2000). Currently, hydration of patients with renal impairment, who undergo angiography, is standard of care in those patients who are able to tolerate the added fluid.

Dopamine and Contrast-Induced Renal Dysfunction

Kapoor et al. (1996) assessed the effects of a dopamine infusion at 5 µg/kg/min on renal function in 40 patients who underwent coronary angiography. Dopamine was given to 20 patients who were randomly selected, while the other group did not receive anything (no placebo). The two groups had similar characteristics of age, gender, baseline ejection fraction (approximately 60%), and dose of contrast agent (approximately 125 ml). The dopamine was initiated 30 minutes before cardiac catheterization and continued for six hours post angiography. The serum creatinine and blood urea nitrogen were followed for 24 hours. The creatinine (M ± SD) was found to be elevated to 1.96 ± 1.2 mg% from 1.52 ± 0.68 mg% and the blood urea nitrogen to 23.25 ± 12.7 mg% from 19.6 ± 13.4 mg% in the group that did not receive dopamine. In 50% of the patients who did not receive dopamine, clinically significant renal impairment (defined as a rise in serum creatinine of 25% or more above baseline) developed within 24 hours of contrast exposure.

Abizaid et al. (1999) tested the effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty through a prospective study of patients with pre-existing renal insufficiency (a serum creatinine equal to or greater than 132.6 μmol/L). Sixty patients who had symptomatic coronary artery disease were randomized to one of three groups: (a) only 0.45% normal saline intravenously at 1 ml/kg/hr, (b) dopamine at 2.5 μg/kg/min and 0.45% normal saline intravenously at 1 ml/kg/hr, or (c) aminophylline 4 mg/kg bolus followed by an infusion of 0.4 mg/kg/hr and 0.45% normal saline intravenously at 1 ml/kg/hr. The patient characteristics in terms of age, gender, hypertension, diabetes mellitus, use of diuretics, NYHA Class II to III heart failure, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, and volume of contrast were similar between the three groups. The exclusion criteria included pre-existing acute renal failure, chronic dialysis therapy, any electrocardiographic or enzymatic evidence of acute myocardial infarction, or an ejection fraction below 20%.

In the first phase of the study patients were hydrated using intravenous 0.45% normal saline at 1 ml/kg/hr starting 12 hours before and continuing for 12 hours after the procedure. Then two hours before cardiac catheterization each group was given the intervention (aminophylline or dopamine). Low osmolality contrast medium was used in all cases. In the second phase of the study patients who developed contrast-induced acute renal failure were re-randomized to receive: (a) 0.45% normal saline intravenously at 1 ml/kg/hr or (b) dopamine 2.5 μg/kg/min and similar intravenous 0.45% normal saline until serum creatinine levels returned to baseline. Serum creatinine was measured 12 hours to 24 hours prior to the procedure and followed twice a day for two days and then daily thereafter until it returned to baseline.

The overall number of patients who developed contrast-induced acute renal failure (defined as an increase in serum creatinine of or greater than 25% above baseline level) was 38% with no significant difference in the incidence of contrast-induced acute renal failure in patients who received intravenous 0.45% normal saline (30%), compared to patients who received dopamine and intravenous 0.45% normal saline (50%), or aminophylline and intravenous 0.45% normal saline (35%). Of the 38% who developed contrast-induced acute renal failure, 65% had diabetes mellitus. The individual volume of contrast varied from 75 ml to 450 ml, but there were no differences in the frequency of acute renal failure when volumes lower than 150 ml were used compared to higher volumes (33% versus 36%, respectively, $\underline{p} = 0.45$). The duration of the hospital stay was similar in those that did not develop contrast-induced acute renal failure (3.1 days), compared to those that did (7.1 days) ($\underline{p} = 0.02$). There were no significant differences in mean (± SD) baseline creatinine levels (203.3 ± 70.7 μmol/L in the saline group, 168.0 ± 27.4 μmol/L in the dopamine group, and 168.0 ± 35.4 μmol/L in the aminophylline group); mean (± SD) peak creatinine levels (247.5 ± 97.2 μmol/L in the saline group, 221.0 ± 53.0 μmol/L in the dopamine group, and 203.3 ± 61.9 μmol/L in the aminophylline group); and mean (± SD) time to peak creatinine levels (2.6 ± 1.4 days in the saline group, 3.3 ± 1.4 days in the dopamine group, and 3.0 ± 1.3 days in the aminophylline group).

Gare et al. (1999) prospectively studied the use of dopamine in protecting against radiocontrast nephropathy in patients with chronic renal failure (a serum creatinine greater than 130 μmol/L) and/or diabetes mellitus who underwent coronary angiography. Patients who had a serum creatinine greater than 200 μmol/L, an acute coronary syndrome within 48 hours, an intolerance to dopamine, or pheochromocytoma were excluded. The study was blinded and one arm received intravenous 0.9% normal saline at 120 ml/day and dopamine 2 μg/kg/min (treatment group), and the other arm received intravenous 0.9% normal saline alone at a similar rate (control group). All patients received intravenous hydration for 8 hours to 12 hours before and 36 hours to 48 hours after angiography with 5% dextrose in 0.45% normal saline at 100 ml/hr or to match urine output. Mannitol was not given to any of the patients in the study, but diuretics, and additional intravenous fluids were permitted at the discretion of the Cardiologist. For the diabetic patients eight units of short acting insulin was added to each 1000 ml of 5% dextrose in 0.45% normal saline and infused at the above rate. Subcutaneous insulin therapy was given, as needed according to blood glucose levels. Urine and blood were collected before angiography, on the first, second, and fifth days after angiography, and at discharge. All patients received nonionic, low osmolality contrast agent.

Sixty-eight patients were entered, but one from each group was withdrawn due to heart failure. The remaining patients were matched based on demographic and clinical characteristics. Six patients, two in the control and four in the treatment group, developed radiocontrast nephropathy, which was defined as an increase in creatinine by 40% from baseline. Serum creatinine (M ± SD) levels before, and on days one, two, and five after angiography were 100.5 ± 6.0 μmol/L, 99.6 ± 6.8 μmol/L, 102.7 ± 6.5 μmol/L, and 117.4 ± 10.6 μmol/L in the control group; and 100.2 ± 6.3 μmol/L, 102.5 ± 7.6 μmol/L, 110.3 ± 9.3 μmol/L, and 113.2 ± 10.9 μmol/L in the treatment group. The patients who developed nephropathy were part of a subgroup of 14 patients (7 in the treatment group and 7 in the control group) who had a higher mean (± SD) baseline creatinine level, 134.4 ± 4.9 μmol/L compared to 91.3 ± 3.3 μmol/L in the other 52 patients ($p < 0.0001$). The creatinine levels (M ± SD) following angiography were 155.6 ± 10.2 μmol/L and 103.9 ± 5.9 μmol/L in the 14 patients and 52 patients, respectively ($p = 0.0002$). There was no significant change in creatinine levels between the two groups, except for the subgroup of patients with peripheral vascular disease. The change in creatinine (M ± SD) was –2.4 ± 2.3 μmol/L in the control and 30.0 ± 12.0 μmol/L in the treatment group ($p = 0.01$). There was no significant difference in the change in creatinine between the two groups in the subgroup of patients with chronic renal failure and diabetes mellitus. Thus there was no benefit with the use of dopamine over hydration; and the use of dopamine worsened renal function in patients with peripheral vascular disease.

Theophylline and Contrast-Induced Renal Dysfunction

Huber, Ilgmann et al. (2002) conducted a prospective double-blinded study on 100 patients with a serum creatinine level of or above 114.9 μmol/L and received a minimum of 100 ml of a low osmolality contrast agent. Patients either received 200 mg of intravenous theophylline over 30 minutes or placebo administered in a similar manner. Patients had to have a stable creatinine, a difference of no greater than 26.5 μmol/L for two days prior to contrast exposure, no previous adverse effects from theophylline, and no history of arrhythmias or seizures. The hydration of these patients was a recommendation of at least two litres a day to be given, but no set protocol was outlined. N-Acetylcysteine 600 mg to 900 mg per day was given to two patients in each group. Serum creatinine was measured at 12 hours, 24 hours, and 48 hours after contrast exposure. Nephropathy was defined as an increase of at least 44.2 μmol/L within 48 hours.

Fifty-four of the 100 patients underwent coronary angiography, while the remainder underwent various other angiographic investigations which included iliofemoral arteriography, cerebrovascular arteriography, celiacomesentericography, transjugular portosystemic shunt placement, and computed tomography. Intra-arterial injection of contrast media took place in 72 of the 100 patients and in all patients more than 150 ml of contrast media was administered. The mean (± SD) serum creatinine levels at baseline was 183.0 ± 83.1 μmol/L versus 169.7 ± 83.1 μmol/L; and the amount of contrast medium administered was 196.5 ± 84.1 ml versus 216.6 ± 95.0 ml in the theophylline group versus the control group, respectively. The overall incidence of contrast material induced nephropathy was 10%, with eight patients (16%) in the placebo group and two (4%) in the theophylline group ($p = 0.046$). The serum creatinine at 24 hours and 48 hours with theophylline decreased to 174.2 ± 66.3 μmol/L ($p = 0.99$) and 171.5 ± 68.1 μmol/L, respectively ($p = 0.99$); and in the control group increased only at 24 hours to 177.7 ± 78.7 μmol/L ($p = 0.006$).

High Dose Contrast Media and Contrast-Induced Renal Dysfunction

In a retrospective review over a six-month period, Khan et al. (1990) found 54 out of 730 patients that underwent coronary angiography received above 400 ml of low osmolality contrast agent. Patients with diabetes mellitus and pre-existing renal insufficiency (serum creatinine above 132.6 µmol/L) received 5% dextrose or 5% dextrose in 0.45% normal saline intravenously the evening before the procedure at a rate of 75 ml/hr to 100 ml/hr. In all others patients hydration was started on the morning of the angioplasty. Typically, a litre of 5% glucose was infused over 10 hours following angioplasty.

The mean (± SD) age of the 54 patients was 63 ± 11 years, with a range from 36 years to 83 years, with 28 patients older than 65 years, 22 had hypertension, 10 had diabetes mellitus, baseline creatinine (M ± SD) was 97.2 ± 17.7 µmol/L with a range from 53.0 µmol/L to 159.1 µmol/L, and four had a baseline creatinine level greater than 132.6 µmol/L, and only one had both diabetes mellitus and pre-existing renal insufficiency. The mean (± SD) dose of contrast was 496 ± 76 ml (range from 400 ml to 785 ml). The mean (± SD) creatinine value rose from 97.2 ± 17.7 µmol/L prior to angioplasty to 106.1 ± 26.5 µmol/L after the procedure ($p = 0.08$). Contrast nephrotoxicity, which was defined as an increase in creatinine greater than 44.2 µmol/L 24 hours to 72 hours following angioplasty, occurred in seven patients; one of who had a rise of above 88.4 µmol/L. Two of these patients had baseline renal insufficiency, two had diabetes mellitus, and one had both. None of these seven patients had an extended hospital stay and creatinine levels were returning to baseline prior to discharge. No patients had oliguria, defined as a urine output below 400 ml/day.

Forced Diuresis and Contrast-Induced Renal Dysfunction

In 1994, Solomon et al. prospectively studied 78 patients with chronic renal failure for acute decreases in renal function induced by contrast media. Renal failure was defined as a serum creatinine exceeding141.4 μmol/L or creatinine clearance rates below 60 ml/min. This cohort was made up of patients who underwent coronary angiography for symptomatic coronary ischemia. All patients received 0.45% normal saline intravenously at a rate of 1 ml/kg/hr 12 hours prior to and 12 hours following the angiography. The patients were randomized to one of three groups: (a) 0.45% normal saline intravenously only, (b) the addition of 25 g of mannitol intravenously 60 minutes before catheterization, or (c) 80 mg of furosemide intravenously 30 minutes before catheterization. Serum creatinine was measured at 12 hours and 24 hours prior to and at the time of angiography, and then daily for two days. Urine was collected for 24 hours following the procedure and urine sodium and potassium were measured.

There was a significant increase in serum creatinine 24 hours following angiography in the mannitol and furosemide group ($p = 0.01$ and $p = 0.02$, respectively) compared to the saline group. At 48 hours the increase in serum creatinine was still seen in the furosemide group. Acute renal dysfunction, defined as a serum creatinine increase by at least 44.2 μmol/L, was 11% in the group that received intravenous 0.45% normal saline only, 28% in the group that received mannitol; ($p = 0.16$ for comparison with the 0.45% normal saline group); and 40% in the group that received furosemide; ($p = 0.02$ for comparison with the 0.45% normal saline group; $p = 0.05$ for the comparison of all three groups). There was no significant difference in ratio of blood urea nitrogen to serum creatinine, total urinary output, or urinary sodium during the initial 24 hours. There was no significant difference between diabetics versus nondiabetics the use versus non-use of calcium channel blockers, or the use of nonionic versus ionic contrast media in the incidence of renal dysfunction.

Stevens et al. (1999) completed a prospective, controlled, single-blinded trial where 98 patients with pre-existing renal insufficiency (serum creatinine greater than 159.1 μmol/L) were randomized to one of two arms. The first arm received intravenous crystalloid (0.45% normal saline at a 150 ml/hr), furosemide (single dose of 1 mg/kg to a maximum of 100 mg), mannitol (12.5 g over two hours if pulmonary capillary wedge pressure below 20 mmHg), and dopamine 3 μg/kg/min. Or to the second arm which received intravenous crystalloid (0.45% normal saline at a 150 ml/hr) and matching placebos. The groups were similar with respect to baseline serum creatinine (M ± SD = 215.7 ± 70.7 μmol/L and 225.4 ± 80.4 μmol/L in the treatment group and control group, respectively), age, weight, diabetic status, left ventricular function, degree of prehydration, contrast volume and ionicity, and extent of peripheral vascular disease. The exclusion criteria included an acute myocardial infarction requiring rescue or primary coronary intervention, the use of vasopressors prior to the procedure, cardiogenic shock, current peritoneal or hemodialysis, or planned post contrast dialysis. Seven cases with urine flow rates below 145 ml/hr in the first 24 hours post procedure required dialysis; two from the experimental arm and five from the control arm. The rates of renal failure in those with urine flow rates above 150 ml/hr post procedure were significantly lower (21.6% versus 45.9%, p = 0.03). The mean individual change in serum creatinine at 48 hours, the primary endpoint, was 42.4 ± 76.0 μmol/L versus 45.1 ± 76.9 μmol/L in the experimental and control arms, respectively (p = 0.87). Both low and high ionic contrast agents were used depending on physician preference with no significant effect on the primary endpoint. Diabetic status, as well, did not have a significant effect on the primary endpoint.

Nonionic Versus Ionic Contrast Media and Contrast-Induced Renal Dysfunction

Davidson et al. (1989) investigated the incidence of cardiovascular and renal toxicity of nonionic agents when used for cardiac catheterization, as well as the value of electrolytes and urinalysis results as predictors of nephropathy induced by a contrast agent. A convenience sample of 1144 patients was enrolled in a nonrandomized trial where renal function and clinical status were evaluated at baseline, and at 24 hours and 48 hours after catheterization. Patients with acute evolving acute myocardial infarction, those having coronary angioplasty, or repeat exposure to contrast media within 48 hours were excluded. The mean (± SD) age of patients was 59.4 ± 11.3 years, with 19.6% having diabetes mellitus, 31.6% having congestive heart failure, and 52.7% having hypertension. Patients without overt congestive heart failure received one litre to one and a half litres of 0.45% normal saline intravenously 8 hours to 12 hours prior to catheterization with an additional 200 ml to 500 ml in the three hours to five hours post catheterization in an attempt to obtain uniform hydration. All patients received iopamidol with an average dose of 203 ± 56 ml. The baseline creatinine (M ± SD) level were 90.2 ± 25.6 µmol/L, increasing to 101.7 ± 30.1 µmol/L at 24 hours, and 107.0 ± 38.9 µmol/L at 48 hours. Contrast-induced nephropathy (defined as a rise in serum creatinine of or above 44.2 µmol/L from baseline within 48 hours) occurred in 6.0%, with 1.4% having an increase of 88.4 µmol/L or greater. No patients developed anuria or oliguria, or required dialysis. The baseline serum creatinine was most significantly associated with the development of nephropathy with the risk rising directly with a level of serum creatinine above 106.1 µmol/L. Contrast-induced nephropathy was not predicted by the fractional excretions of sodium, the uric acid excretion, urinary uric acid to creatinine ratio, or by crystalluria. The most frequent cardiotoxicity effect was chest pain of less than 10 minutes in duration without electrocardiographic changes.

In 1989, Schwab et al. investigated the benefits of nonionic contrast agents compared to ionic agents in patients undergoing cardiac catheterization. Patients (n = 443) were stratified into low risk or high risk groups based upon the presence of diabetes mellitus (treated with either insulin or an oral agents), congestive heart failure (based on clinical examination), or pre-existing renal insufficiency (a serum creatinine level above 133 µmol/L). Once randomized, all patients received intravenous prehydration of one litre to one and a half litres of 5% dextrose in 0.45% normal saline initiated the night before cardiac catheterization and continued for four hours afterward at a rate of 125 ml/hr. Diuretic agents and nonsteroidal anti-inflammatory drugs were withheld unless clinically indicated, and nephrotoxic antibiotics were not administered. Diatrizoate and iopamidol were used exclusively, with the mean (± SD) dose being 171 ± 53 ml. Serum creatinine and urine creatinine were measured before, and at 24 hours and 48 hours after catheterization. Contrast nephrotoxicity was defined as an increase in the serum creatinine level of at least 44.2 µmol/L above the baseline value within 48 hours. This study did not demonstrate a statistically significant difference in the creatinine levels between contrast agents (10.2% in patients receiving diatrizoate, and 8.2% in patients receiving iopamidol).

Taliercio et al. (1991) conducted a double-blind, randomized controlled trial that involved 307 high risk patients with renal impairment (serum creatinine above or equal to 132.6 µmol/L) undergoing cardiac catheterization, to compare nephrotoxicity effects of iopamidol to diatrizoate. Patients were excluded if there was significant heart failure, severe aortic stenosis, receiving nephrotoxic drugs, clinical indications to consider a low osmolarity agent, exposure to additional contrast agent, or major surgery soon after coronary angiography. Patients were hydrated orally until midnight before cardiac catheterization, and if they were unable to maintain oral intake, intravenous fluids were initiated the night before the cardiac catheterization. Serum creatinine was measured prior to the administration of contrast and then at 24 hours. Further serum creatinine measurements were made based on clinical evidence of acute renal dysfunction. The mean age of the patients was 68 years with a mean serum creatinine of 178.6 μmol/L. The groups were well matched in terms of medication usage, heart failure, hypertension, diabetes mellitus, coronary artery disease, and peripheral vascular disease. The mean (± SD) increase in serum creatinine 24 hours after angiography was 9.7 ± 17.7 μmol/L in the iopamidol group compared to 19.5 ± 23.0 μmol/L in the diatrizoate group ($p < 0.001$). There was a greater than 44.2 μmol/L increase in serum creatinine at 24 hours in 5% of the iopamidol group compared with 11% in the diatrizoate group ($p = 0.07$). Acute renal failure, defined as a maximal increase in serum creatinine greater than 88.4 μmol/L, occurred in 3% compared to 7% receiving iopamidol and diatrizoate, respectively ($p = 0.16$).

In a prospective, double-blind, randomized study of 70 patients with normal to mildly depressed renal function (serum creatinine of or below 175 μmol/L), Katholi et al. (1993) compared the renal effects of ionic high osmolality to nonionic low osmolality agents. Patients undergoing cardiac catheterization with unstable hemodynamics, taking nephrotoxic medication (angiotensin converting enzyme inhibitors, beta-adrenergic receptor antagonists, nonsteroidal anti-inflammatory agents, digoxin, allopurinol, theophylline, xanthine-containing agents, or dipyridamole), unstable angina, recent acute myocardial infarction, clinically evident congestive heart failure, an ejection fraction of less than 40%, known valvular disease, uncontrolled hypertension (systolic above 180 mmHg, and diastolic above 100 mmHg), or a known allergy to contrast were excluded. All patients were maintained on a two to four grams-sodium restricted diet, and hydration throughout the three days of study at a minimum of 1.43 ml/kg/hr with either oral fluids or 5% dextrose intravenously. A 12-hour urine collection with a serum creatinine at the end of the 12 hours was collected prior to, as well as, for two days following catheterization. The two groups, ionic versus nonionic, were well matched with regard to age, weight, arterial pressure, baseline sodium secretion, baseline urine flow, diabetes mellitus, and proteinuria. In the nonionic group, creatinine clearance (M ± SD) decreased from 83 ± 18 ml/min to 61 ± 15 ml/min at 24 hours to full recovery at 48 hours. In the ionic group, creatinine clearance (M ± SD) decreased from 82 ± 19 ml/min to 46 ± 16 ml/min at 24 hours and remained depressed at 43 ± 15 ml/min at 48 hours. The differences in serum creatinine levels were not statistically significant in either group at any time.

Hemodynamically stable, high and low risk patients (based on the presence of diabetes and/or renal insufficiency), who were referred for nonemergent diagnostic cardiac angiography, were enrolled in a randomized prospective study to compare the incidence of contrast nephrotoxicity between nonionic and ionic contrast agents (Rudnick et al., 1995). Patients (n = 1196) were stratified into one of four groups: (a) nondiabetic, serum creatinine less than 132.6 µmol/L, (b) diabetic, serum creatinine less than 132.6 µmol/L (c) nondiabetic, serum creatinine equal or greater than 132.6 µmol/L, and (d) diabetic, serum creatinine equal or greater than 132.6 μmol/L. Within each group, patients were randomized to receive either nonionic or ionic contrast agents. Patients who had recently received iodinated contrast media or nephrotoxic agents, had undergone recent surgery, had acute renal failure, malignant hypertension, or a recent change in dosage of diuretics, antihypertensives, or calcium channel antagonists were excluded. Intravenous 5% dextrose in 0.45% normal saline at a recommended rate of 100 ml/hr was administered, beginning at least four hours prior to angiography and continued for 24 hours post procedure, unless clinically contraindicated. The primary outcome for this study was an increase in serum creatinine of 88.4 μmol/L or more from baseline within 48 hours to 72 hours following contrast administration. The mean (± SD) contrast volume was similar in both groups with 140.0 ± 56.6 ml in the iohexol group and 139.1 ± 54.9 ml in the diatrizoate group, ($p = 0.83$). In those patients that received diatrizoate 7.1% compared to 3.2% receiving iohexol, met the primary outcome ($p = 0.002$). Using a secondary definition of nephrotoxicity of an increase in the baseline serum creatinine value equal or greater than 44.2 μmol/L within 48 hours to 72 hours after contrast administration showed an increased incidence of nephrotoxicity in all groups. But this did not change the significant differences in nephrotoxicity between iohexol group and diatrizoate group (13.4% compared to 21.1%, respectively, $p < 0.001$).

Patients referred for coronary or aortofemoral angiography who had diabetes, older than 18 years of age, and had a stable serum creatinine concentration of 133 μmol/L to 308 μmol/L for men and 115 μmol/L to 308 μmol/L for women within the previous three months or a creatinine clearance of less than 60 ml/min were considered for enrolment into a multicenter trial by Aspelin et al. (2003). Patients were excluded if they had received contrast within seven days, treated with metformin or nonsteroidal anti-inflammatory drugs within 48 hours, use of nephrotoxic drugs within seven days, newly diagnosed unstable diabetes mellitus, renal transplantation, on dialysis therapy, or had severe concomitant disease. Patients were prospectively randomized into a double-blind, controlled trial in which one arm received iodixanol and the other arm received iohexol. All patients were well hydrated according to local regimens. It was recommended, but not required that patients receive 500 ml of water orally, 500 ml of 0.9% normal saline intravenously, or both before angiography. This was then followed by one litre of 0.9% normal saline intravenously that started at the beginning of the procedure. The volume of contrast varied according to the type of diagnostic testing completed. The follow-up period was seven days with the primary end point of a peak increase in serum creatinine between day zero and day three. There were three secondary end points: (a) the number of patients with peak increase of at least 44.2 μmol/L, (b) the number of patients with a peak increase of at least 88.4 μmol/L during day zero through day three, (c) and finally a change in creatinine from day zero to day seven. One hundred twenty-nine patients were enrolled with 64 receiving iodixanol and 65 receiving iohexol. Both groups were matched on baseline characteristics. The peak increase in creatinine within three days was 11.5 μmol/L in the iodixanol group compared to 48.6 μmol/L in the iohexol group ($\underline{p} = 0.001$). The effect of baseline creatinine on the level of increase in creatinine was different in the two groups. In the iohexol group a higher baseline creatinine was associated with a higher peak increase between day zero and day three ($\underline{p}$ for interaction < 0.001). The iodixanol group was significantly less nephrotoxic than the iohexol group with a mean change in creatinine between day zero and day seven of 6.2 μmol/L and 21.2

µmol/L, respectively (p = 0.003). Based on the definition of nephropathy, the incidence was 3% in the iodixanol group (2 out of 64) and 25% in the iohexol group (17 out of 65) (p = 0.002).

Fenoldopam and Contrast-Induced Renal Dysfunction

Madyoon (2001) published a retrospective review of 46 consecutive cases, which underwent coronary angiography treated with fenoldopam. The patients enrolled required a previous diagnosis of diabetes with a serum creatinine at or above 132.6 µmol/L or no diabetes with a serum creatinine at or above 150.3 µmol/L. This group received intravenous fenoldopam two hours prior to contrast exposure at a dose of 0.1 µg/kg/min, and it was titrated up every 20 minutes to a maximum dose of 0.5 µg/kg/min, as long as the systolic blood pressure was greater than 100 mmHg and the diastolic blood pressure remained within 20 mmHg of baseline. All patients received iohexol (M ± SD volume of 141 ± 84 ml). The baseline serum creatinine (M ± SD) was 212.2 ± 88.4 µmol/L with a range from 132.6 µmol/L to 645.3 132.6 µmol/L in the fenoldopam group. The historical comparator group (n = 50) received intravenous 0.9% normal saline with either dopamine (30% of group), mannitol (20% of group), or atrial natriuretic peptide (20% of group). All patients in the historical group received diatrizoate with a mean (± SD) volume of 124 ± 6 ml and had a baseline serum creatinine (M ± SD) of 221 ± 8.8 µmol/L. The incidence of acute renal failure, defined as a 25% increase in creatinine at 48 hours, was 13% (6 out of 46) compared to 38% (19 out of 50), in the fenoldopam group and comparator group, respectively. The incidence of acute renal failure was 14% in the diabetic group who received fenoldopam, compared to 67% in the comparator group.

In a randomized, prospective study to compare the efficacy of N-Acetylcysteine or fenoldopam and hydration, 123 patients who underwent cardiovascular interventions were enrolled by Allaqaband et al. (2002). All patients had a baseline creatinine of 141.4 μmol/L or greater or a creatinine clearance of or less than 60 ml/min. This cohort received low osmolality nonionic contrast media. Patients who underwent cardiac angiography, and in some cases concomitant angioplasty, received ioversol, while those who underwent peripheral vascular studies received iodixanol. There were three arms to which a patient could be randomized: (a) intravenous 0.9% normal saline only, (b) intravenous 0.9% normal saline and N-Acetylcysteine 600 mg orally twice daily for four doses beginning the day before the procedure, or (c) intravenous 0.9% normal saline and intravenous fenoldopam at 0.1 μg/kg/min starting four hours before and continuing for four hours following the procedure. No patients received aminophylline, theophylline, or dopamine during the study period. There was no statistically significant difference between the three groups or change in serum creatinine at 24 hours or 48 hours after contrast exposure. The incidence of nephropathy (defined as an increase of 44.2 μmol/L within 48 hours) occurred in 17.7% of the N-Acetylcysteine group, in 15.3% of the normal saline only group, and in 15.7% of the fenoldopam group. Of the 20 patients who developed nephropathy, two (1.62% of all patients enrolled) needed dialysis. Allaqaband et al. stated that previous studies with the use of both N-Acetylcysteine and fenoldopam to date had shown a benefit that their study failed to reproduce.

Hemodialysis and Contrast-Induced Renal Dysfunction

Vogt et al. (2001) studied the efficacy of hemofiltration in 113 patients with chronic stable renal failure (serum creatinine greater than 200 μmol/L). The renal failure was secondary to diabetic nephropathy, hypertension, nephroangiosclerosis, glomerulonephritis, tubulointerstitial nephritis, and chronic graft dysfunction. Patients underwent various angiographic studies that included renal angioplasty, peripheral vascular imaging, and computed tomography, with 38 of the patients undergoing coronary angiography. No patients received N-Acetylcysteine, theophylline, dopamine, mannitol, or furosemide throughout the study. A nonionic low osmolality contrast agent was used with a volume of 20 ml to 740 ml (M ± SD = 176 ± 133ml). Patients were assigned randomly to receive 0.9% normal saline intravenously at 1 ml/kg/hr for 12 hours before and after angiography; or 0.9% normal saline intravenously before angiography and hemofiltration after angiography. The primary end points were acute radiocontrast nephropathy within one to six days after contrast exposure, need for dialysis, or cardiovascular complications (i.e., myocardial infarction, pulmonary edema, stroke). Secondary end points were a maximum increase of creatinine above 132 μmol/L or a greater than 50% increase above baseline creatinine. The end points of those who were randomized to receive hemofiltration also included arteriovenous fistulae, thrombosis, and infection at the puncture site. The baseline creatinine (M ± SD) was 308 ± 106 μmol/L (control group) and 316 ± 112 μmol/L (hemofiltration group) ($p = 0.69$). The estimated creatinine clearance (M ± SD) in the hemofiltration group was 20 ± 7 ml/min and 22 ± 8 ml/min in the control group. Two patients died during the first day due to sudden cardiac death and an acute coronary occlusion. In the control group ($n = 53$), creatinine levels (M ± SD) peaked at 322 ± 126 μmol/L 96 hours after contrast exposure compared to baseline creatinine levels ($p = 0.98$). In the hemofiltration group ($n = 52$), creatinine levels (M ± SD) decreased to 277 ± 95 μmol/L at 24 hours and peaked to 353

± 126 μmol/L at 96 hours following angiography compared to baseline creatinine levels (p = 0.04). With patients who received greater than 150 ml of contrast agent, no beneficial effects of hemofiltration were seen on creatinine levels. Twenty-two of the 111 patients (9 in the control and 13 in the hemofiltration, p = 0.35) required permanent dialysis therapy. A 50% or greater reduction in renal function from baseline at anytime during the study period occurred in 11 patients, with 6 in the control and 5 in the hemofiltration groups (p = 1.0). A total of 21 patients (19% of the total cohort) experienced a clinical event. These events included nephropathy requiring dialysis, cardiovascular event, death, or dialysis related complications. There were 8 in the control group and 13 in the hemofiltration group (p = 0.23). The study determined that hemofiltration did not decrease the rate of complications in patients following angiography, including nephropathy.

Huber, Jeschke et al. (2002) completed a prospective study to determine the efficiency of dialysis in preventing contrast-induced nephropathy at 48 hours. Thirty-one patients with severely impaired renal function (a serum creatinine greater than 221.0 μmol/L or a creatinine clearance below 30 ml/min) were included. Patients with a serum creatinine levels between 114.9 μmol/L to 212.2 μmol/L were also included if they had at least two additional risk factors for contrast-induced nephropathy. These risk factors included diabetes mellitus, dehydration, high dose on contrast media, plasmocytoma, nephrotoxic medications, age greater than 70 years, arterial hypertension, proteinuria, arterial contrast injection, liver dysfunction, heart failure, previous contrast exposure, and hyponatremia. Twenty-five of these 31subjects underwent coronary angiography. There was no comparator group in this study.

The reason for renal impairment was diabetic nephropathy in 13 patients, hypertensive nephropathy in 7 patients, and chronic glomerulonephritis in 8 patients. Of the remaining three patients one had hepatorenal syndrome, one had unilateral nephrectomy and lastly, one had persistent stable renal impairment after acute renal failure. The baseline serum creatinine (M ± SD) was 354.5 ± 161.8 µmol/L, with a range from 123.8 µmol/L to 804.4 µmol/L, with a corresponding creatinine clearance (M ± SD) of 22.6 ± 10.3 ml/min. The mean (± SD) volume of low osmolality contrast media given was 278.4 ± 160.5 ml. The period of dialysis (M ± SD) lasted 4.36 ± 1.0 hours and 11 (35%) patients developed side effects attributable to dialysis therapy, which included circulatory instability, bleeding complications, and catheter-related hematomas. Despite dialysis 19 out of the 31 patients (61%) met the primary end point and developed an increase in creatinine levels of at least 44.2 µmol/L within seven days. Of these 19 patients, 14 of them had a significant increase in serum creatinine of or greater than 44.2 µmol/L within the first three days.

Dialysis was shown to be effective in lowering serum creatinine levels (M ± SD) immediately to 198.9 ± 129.1 µmol/L and one day after contrast exposure to 304.1 ± 137.0 µmol/L compared to baseline. In the subgroup of patients who developed contrast-induced nephropathy, serum creatinine levels (M ± SD) were significantly lower after dialysis at 212.2 ± 152.1 µmol/L compared to baseline levels of 388.1 ± 183.0 µmol/L. There was, however, no significant difference compared with baseline after two days. Twelve of the 19 patients (63%) had their maximum serum creatinine concentration within the first 5 days of contrast media exposure with a maximum increase of 44.2

μmol/L to 88.4 μmol/L in 7 patients and greater than 88.4 μmol/L in 12 patients. Four patients needed repeat dialysis therapy within seven days of angiography; and renal function did not improve in two of these patients. Among the patients with contrast-induced nephropathy, but without a need for repeat dialysis (n = 15), serum creatinine at discharge was at least 44.2 μmol/L above baseline.

To prospectively evaluate the effectiveness of continuous veno-venous hemofiltration in treating patients who develop oligo-anuric acute renal failure after contrast exposure, Marenzi, Bartorelli et al. (2003) enrolled 33 consecutive patients, who had undergone percutaneous coronary intervention. All patients received low osmolality nonionic contrast media and received a continuous intravenous infusion of furosemide at 500 mg to 1000 mg/24 hours and dopamine at 2 μg/kg/min in addition to continuous veno-venous hemofiltration. There was no comparison group. The baseline serum creatinine (M ± SD) was 161.8 ± 53.0 μmol/L with a creatinine clearance (M ± SD) of 46 ± 17 ml/min. Pre-existing chronic renal insufficiency, defined as a serum creatinine above 132.6 μmol/L was present in 67% of the cohort. Thirteen patients had complications during percutaneous coronary intervention, which included ventricular fibrillation, acute pulmonary edema, cardiogenic shock, severe bleeding, and prolonged systemic hypotension. The mean (± SD) contrast volume used was 244 ± 138 ml. Before receiving continuous veno-venous hemofiltration therapy all patients had oligo-anuria for 48 hours to 96 hours, with 20 of them having heart failure and 13 of them having no heart failure.

The mean serum creatinine at 24 hours in this study cohort was 353.6 μmol/L with a decrease to 176.8 μmol/L at the time of discontinuation of continuous veno-

venous hemofiltration. The creatinine clearance increased from 20 ml/min to 30 ml/min from 24 hours to the end of continuous veno-venous hemofiltration therapy. The mean (± SD) time to initiation of continuous veno-venous hemofiltration was 76 ± 15 hours with the mean (± SD) duration of therapy 4.7 ± 2.6 days. Patients had a mean (± SD) body fluid reduction of 75 ± 48 ml/hr and a mean (± SD) fluid volume replacement of 1000 ± 247 ml/hr. There was no associated hypotension with continuous veno-venous hemofiltration therapy. Those patients who had fluid overload had their volume status corrected within 24 hours. There was an in-hospital mortality of 9.1% (n = 3) during continuous veno-venous hemofiltration therapy secondary to multi-system organ failure and refractory cardiogenic shock. In all but one patient, diuresis returned, and in this single patient permanent dialysis was required.

One hundred fourteen patients who were scheduled for coronary angiography or elective percutaneous coronary intervention were enrolled in a study by Marenzi, Marana et al. (2003) to assess the efficacy of hemofiltration in preventing contrast agent induced nephropathy. These patients had chronic renal failure defined as a serum creatinine greater than 176.8 µmol/L and a creatinine clearance less than 50 ml/min. Patients who had an acute coronary syndrome, cardiogenic shock, peritoneal or hemodialysis, overt congestive heart failure, recent major bleeding, or contraindication to anticoagulation therapy were excluded. All patients received a low osmolality nonionic contrast agent and no renoprotective drugs were administered. Patients were randomized to receive either intravenous 0.9% normal saline at 1 ml/kg/hr (0.5 ml/kg/hr, if their ejection fraction was less than 40%) for 6 to 8 hours before and 24 hours post coronary angiography. Or patients were randomized to undergo hemofiltration, which was initiated four to six hours before the procedure and resumed after completion of the procedure, and continued for 18 hours to 24 hours before being discontinued. Blood urea nitrogen and creatinine levels were measured at baseline, immediately before angiography, at the end of the treatment, then daily for three days and prior to discharge.

Both groups were matched with severe renal failure. The creatinine clearance (M ± SD) in the hemofiltration group was 26 ± 9 ml/min and 26 ± 8 ml/min in the control group ($p = 0.63$), and the creatinine levels (M ± SD) were 265.2 ± 88.4 μmol/L and 274.0 ± 88.4 μmol/L in the hemofiltration group and control group, respectively ($p = 0.84$). In the hemofiltration group, one patient developed shock post hemodialysis, three patients developed bleeding which required transfusions, and two required staged procedures – one because of complex anatomy, and the second developed atrial fibrillation with a rapid ventricular response during the initial procedure. There was a statistically significant increase in mean creatinine and blood urea nitrogen in the control group and these measures remained above baseline at the time of discharge. These same measures were found to decrease in the hemofiltration group and progressively returned to baseline at discharge. The increase in serum creatinine in the control group was significant on days two, three, and at discharge ($p < 0.001$). The decrease in serum creatinine from baseline in the hemofiltration group was significant the day of procedure, and on days one, two, and three, and at discharge ($p < 0.001$). Emergency dialysis was required in 10 patients in the control group due to pulmonary edema, but none in the hemofiltration group. In-hospital mortality was significantly lower in the hemofiltration group with only one death due to cardiogenic shock, whereas eight deaths occurred secondary to acute myocardial infarction complicated by shock, multi-system organ failure, and refractory heart failure, in the control group (2% versus 14%, respectively, p = 0.02).

N-Acetylcysteine and Contrast-Induced Renal Dysfunction

Tepel et al. (2000) first investigated the effects of prophylactic oral administration of N-Acetylcysteine with hydration in reducing CIRD secondary to a nonionic, low osmolality contrast agent (iopromide) administration in patients with chronic renal insufficiency. This prospective study included 83 patients with chronic renal failure with stable serum creatinine concentrations above 106.1 μmol/L or creatinine clearance of below 50 ml/minute (0.8 ml/sec) who underwent elective computed tomography for the evaluation of abdominal or thoracic illnesses. The mean (± SD) serum creatinine was 212.2 ± 114.9 μmol/L in this noncardiac cohort; and both groups were similar on all other baseline characteristics. N-Acetylcysteine 600 mg twice daily was given orally on the day before and the day of the procedure, for a total of two days. Intravenous 0.45% normal saline was given at a rate of 1 ml/kg/hr for 12 hours before and 12 hours after the administration of the contrast agent. Serum creatinine levels were measured immediately before, at 48 hours, and then six days after administration of the contrast agent (contrast dose = 75 ml). No patients received theophylline, dopamine, mannitol, or furosemide during the study. Acute contrast agent induced reduction in renal function, defined as an increase of at least 44.2 μmol/L in the serum creatinine concentration 48 hours after administration of the contrast agent, occurred in 12% of patients; 2% in the N-Acetylcysteine group and 21% in the control group (p = 0.01; relative risk = 0.1; 95% confidence interval 0.02 to 0.9). Of the 10 patients who developed renal dysfunction secondary to contrast exposure five of them had a diagnosis of diabetes. The N-

Acetylcysteine group had a significant ($p < 0.001$) decrease in mean (± SD) serum creatinine concentrations from 221.0 ± 114.9 μmol/L to 185.6 ± 114.9 μmol/L 48 hours after administration of contrast agent. In the control group no changes in mean serum creatinine concentrations were observed.

Since publication of this data, the administration of N-Acetylcysteine has been increasing in patients with chronic renal insufficiency and associated risk factors as a prophylactic measure to decrease the incidence of CIRD. A literature search to date revealed several trials comparing N-Acetylcysteine and hydration against placebo and other therapies and hydration in reducing the incidence of renal dysfunction in patients undergoing elective coronary angiography. Diaz-Sandoval, Kosowsky, and Losordo (2002) conducted a randomized, double-blind, placebo, controlled trial to investigate the effects of four doses of 600 mg orally administrated N-Acetylcysteine versus placebo. Patients ($n = 54$) with stable chronic renal insufficiency (a serum creatinine of or above 123.8 μmol/L or a creatinine clearance less than 50 ml/min) undergoing elective cardiac catheterization had two measurements of renal function the week preceding cardiac catheterization with follow-up measurements at 24 hours and 48 hours following cardiac catheterization. Patients were excluded if there was hemodynamic instability (systolic blood pressure below 90 mmHg or diastolic below 50 mmHg), untreated gastrointestinal bleeding, or treatment with theophylline, mannitol, ciprofloxacin, and/or trimethoprim-sulfamethoxazole. N-Acetylcysteine was dosed twice daily with one dose before and three doses following angiography. All patients received intravenous 0.45% normal saline at 1 ml/kg/hr for 2 hours to 12 hours before and 12 hours after cardiac catheterization with low osmolality contrast agent. The baseline and clinical characteristics of the two groups were similar. The volume of contrast agent (ioxilan and iodine) was similar in both groups (*M* ± SD = 189 ± 12 ml in the placebo group and 179 ± 8 ml in the treatment group, $p = 0.4$). The primary end point, increase in serum creatinine of or greater than 44.2 μmol/L or greater than 25% above baseline 48 hours after catheterization, occurred in 45% of the placebo group and 8% of the N-Acetylcysteine group ($p = 0.005$; relative risk = 0.21; 95% confidence interval 0.06 to 0.8). The mean (± SD) serum creatinine increased from 137.9 ± 4.4 μmol/L to 166.9 ± 8.0 μmol/L 48 hours after cardiac catheterization in the placebo group, whereas in the N-Acetylcysteine group the mean (± SD) creatinine decreased from 146.7 ± 5.3 μmol/L to 135.3 ± 8.0 μmol/L ($p < 0.0001$). Peripheral vascular disease, renal artery stenosis, and contrast dose greater than 220 ml were associated with an increase in serum creatinine ($p < 0.05$).

Another study investigating the effects of N-Acetylcysteine on CIRD by Briguori et al. (2002) involved 183 consecutive patients with renal impairment undergoing elective coronary and/or peripheral angiography and/or angioplasty. Renal impairment was defined as a serum creatinine greater than 106.1 μmol/L and/or an estimated creatinine clearance below 70 ml/min. Patients were randomized to receive oral N-Acetylcysteine 600 mg twice daily on the day before and the day of coronary angiography, and 12 hours of intravenous 0.45% normal saline before and after the procedure or intravenous 0.45% normal saline alone for a similar duration of time. None of the patients received theophylline, dopamine, mannitol, or furosemide. Serum creatinine and urea were measured immediately before contrast agent administration and 48 hours after contrast agent administration; and the creatinine clearance was calculated using the Cockcroft-

Gault formula. A urinalysis was done the day before contrast agent administration to assess for proteinuria. An early contrast agent induced reduction in renal function was defined as an increase in the serum creatinine concentration of or greater than 25% of the baseline value at 48 hours or the need for dialysis after the administration of the contrast agent. The mean (± SD) serum creatinine concentration for all patients was 134.4 ± 35.4 μmol/L, with a range from 110.5 μmol/L to 427.9 μmol/L. The amount of contrast agent administered was similar with 194 ± 127 ml in the treatment group, and 200 ± 144 ml in the control group ($p = 0.8$). The amount of contrast agent (M ± SD) was significantly higher ($p < 0.001$) in patients who had ad-hoc percutaneous coronary intervention (M ± SD = 347 ± 182 ml). In the group that received the N-Acetylcysteine (treatment group), the mean (± SD) serum creatinine decreased from 134.4 ± 38.0 μmol/L to 130.8 ± 31.8 μmol/L 48 hours after contrast agent administration. In those patients that received intravenous hydration alone (control group) the serum creatinine did not change. There was no statistically significant interaction between the changes in serum creatinine and the treatment strategy ($p = 0.87$). Acute contrast agent nephrotoxicity occurred in 6.5% of the N-Acetylcysteine group and in 11% of the intravenous hydration group ($p = 0.22$). Only one patient from the hydration alone group required temporary dialysis. The amount of contrast agent used was a predictor of acute renal function deterioration (odds ratio = 2.58; 95% confidence interval 1.1 to 4.9; $p = 0.035$). A volume of contrast above or equal to 140 ml was the best cutoff value to predict the occurrence of contrast associated nephrotoxicity.

The study by Shyn, Cheng, and Kuan (2002) evaluated 121 patients with chronic renal insufficiency (defined as a serum creatinine above 176.8 μmol/L and below 530.4

µmol/L, or a creatinine clearance less than 40 ml/min but greater than 8 ml/min) scheduled for cardiac angiography for the incidence of CIRD. The mean (± SD) serum creatinine was 247.5 ± 70.7 µmol/L in this sample. Patients were excluded from the study if they had an acute myocardial infarction requiring primary or rescue coronary intervention, use of vasopressors before the procedure, cardiogenic shock, current peritoneal dialysis or hemodialysis, planned post contrast dialysis, or allergies to the study medications. None of the patients received theophylline, dopamine, or mannitol during the study. N-Acetylcysteine was given orally 400 mg twice daily on the day before and the day of the procedure in the treatment group, along with intravenous 0.45% normal saline at a rate of 1 ml/kg/hr for 12 hours before and 12 after following coronary angiography. The control group received similarly scheduled placebo dosing and intravenous hydration. All patients were encouraged to drink if they were thirsty. Serum creatinine and blood urea nitrogen were measured 12 hours to 24 hours before, and at 48 hours, and seven days following angiography. Both groups were well matched in terms of clinical and biochemical characteristics. The volume of contrast agent (M ± SD) (iopamidol) used was 119 ± 3 ml in the treatment group, and 115 ± 48 ml in the control group. In the control group, the mean (± SD) serum creatinine increased from 247.5 ± 70.7 µmol/L to 274.0 ± 88.4 µmol/L at 48 hours ($p < 0.01$). In the treatment group, the mean (± SD) serum creatinine decreased from 247.5 ± 70.7 µmol/L to 221.0 ± 88.4 µmol/L at 48 hours ($p < 0.01$). Acute contrast-induced reduction in renal function, defined as an increase in the serum creatinine of at least 44.2 µmol/L at 48 hours after exposure to contrast agent, occurred in 13.2% of the sample population, with 3.3% in the treatment group, and 24.6% in the control group ($p < 0.001$; relative risk 0.13; 95% confidence interval 0.08 to 0.20).

Durham et al. (2002) enrolled 81 patients who were referred for cardiac angiography (diagnostic and therapeutic procedures) who had a baseline serum creatinine above 150.3 μmol/L to determine the efficacy of N-Acetylcysteine in decreasing the incidence of contrast nephropathy. Patients were excluded if they were below 18 years, found to have a reversible component to their renal impairment, evidence of atheroembolic disease, severe asthma, peptic ulcer disease, or respiratory depression. Patients were randomized to one of two arms: (a) 1200 mg of oral N-Acetylcysteine with the first dose given one hour before and the last dose given three hours following angiography plus intravenous hydration up to 12 hours before angiography and for 12 hours following angiography, or (b) placebo dosed in a similar manner with the same hydration protocol. Both arms used 0.45% normal saline at 1 ml/kg/hr for the intravenous hydration. Durham et al. recorded serum creatinine immediately after catheterization, at 48 hours, and at 144 hours post contrast exposure, volume of contrast, and total intravenous hydration. Two patients were lost to follow-up because of immediate discharge from the hospital. The 79 remaining patients were matched on baseline parameters. The indication for angiography was an acute coronary syndrome in only 15 of the 79 patients. The mean (± SD) baseline serum creatinine was 203.3 ± 44.2 μmol/L in the placebo group and 194.5 ± 35.4 μmol/L in the N-Acetylcysteine group. The mean (± SD) contrast volume was 84.7 ± 42.1 ml and 77.4 ± 35.9 ml; and the volume of hydration (M ± SD) received was 1061 ± 442 ml and 1255 ± 713 ml, in the placebo group and N-Acetylcysteine group, respectively. Acute renal failure occurred in

19 or 24% of the patients (defined as an increase of 44.2 μmol/L in serum creatinine), with an increase in serum creatinine above 88.4 μmol/L in five patients and an increase of above 176.8 μmol/L in two patients, both of who required dialysis. There was no statistically significant difference between the groups (9 out of 41 in the placebo group (22%), and 10 out of 38 in the N-Acetylcysteine group (26.3%). In patients with diabetes mellitus there was a nonsignificant increase in the risk of renal failure in the patients treated with N-Acetylcysteine.

In an abstract by Adamian et al. (2002), 57 consecutive patients, who underwent percutaneous coronary intervention, with baseline serum creatinine levels above 132.6 μmol/L and below 300.6 μmol/L, but did not require dialysis, were investigated for contrast nephropathy. Thirty-five patients received oral mucomyst 600 mg twice daily with intravenous hydration, while 22 patients received intravenous hydration only. The hydration protocol was not described. All patients received iodixanol with a volume (M ± SD) of 273 ± 113 ml in the treatment group and 303 ± 152 ml in the control group. The baseline creatinine (M ± SD) was 167.1 ± 38.9 μmol/L and 173.3 ± 44.2 μmol/L; and was 166.2 ± 88.4 μmol/L and 219.2 ± 114.9 μmol/L at 48 hours following contrast exposure in the treatment group and control group, respectively. Contrast-induced nephropathy occurred in 2.9% of the treatment group and 36.4% in the control group ($p = 0.002$). Dialysis therapy was required for 2.9% in the treatment group and 13.7% in the control group ($p = 0.29$).

A prospective, randomized, double-blind, placebo, controlled trial was conducted by Oldemeyer, Biddle, Wurdeman, Mooss, Cichowski, and Hilleman (2003) on 96 patients, with a baseline creatinine clearance of or below 50 ml/min, and a serum creatinine of or greater than 106.1 µmol/L who were scheduled for coronary angiography with or without concomitant percutaneous coronary intervention with an anticipated contrast agent load of or greater than 75 ml. Patients were excluded if they were in acute renal failure, undergoing dialysis, unstable renal function (as evidenced by change in creatinine of or greater than 44.2 µmol/L or equal to or greater than 25% in the prior ten days), administration of mannitol, intravenous catecholamines, parental diuretics, theophylline, or contrast agent within seven days, mechanical ventilation, cardiogenic shock, or emergent angiography. All patients received 0.45% normal saline at 1 ml/kg/hr for 12 hours before and 12 hours following angiography and either received placebo or oral N-Acetylcysteine 1500 mg every 12 hours starting the evening before angiography, for a total of four doses. The use of nonionic low osmolality contrast media was constant in this cohort of study patients. The clinical characteristics of the cohort were similar between the study groups. The baseline serum creatinine (M ± SD) was 144.1 ± 71.6 µmol/L and 146.7 ± 57.5 µmol/L, in the treatment group and placebo group, respectively. The serum creatinine decreased to 137.9 µmol/L and 136.1 µmol/L in the treatment group and placebo group, respectively, at 24 hours and then increased to 142.3 µmol/L in both groups at 48 hours. Contrast-induced nephropathy (defined as an absolute increase in serum creatinine of or greater than 44.2 µmol/L, or a relative increase of or greater than 25% in serum creatinine at 24 hours or 48 hours following the procedure) occurred in 8.2% (4 out of 49 of the patients) in the N-Acetylcysteine group and in 6.4% (3 out of 47 of the patients) in the placebo group ($p = 0.74$). Stepwise logistic regression identified volume of contrast ($p = 0.007$) and urea ($p = 0.008$) as the only independent predictors of contrast-induced nephropathy. The amount of contrast volume (M ± SD) in the group with nephropathy was 180.0 ± 25.9 ml compared to 127.1 ± 68.9 ml in the group without nephropathy. Baseline urea levels (M ± SD) were 46.3 ± 25.9 mg/dl in the patients with nephropathy and 32.4 ± 14.4 mg/dl in the patients without nephropathy. The changes in serum creatinine were not significant and changes at 24 hours and 48 hours in creatinine levels were not reported; and no patients required dialysis. Contrast-induced nephropathy occurred in 12% (5 of 43 diabetic patients) and 4% (2 of the 52 non-diabetic patients) ($p = 0.15$). With the increase in dosage of N-Acetylcysteine there were side effects seen, which were noted to occur in 16% of the patients. These effects were predominantly gastrointestinal (i.e., nausea, stomach ache, discomfort, diarrhea, constipation), but one incidence of headache and another of chest tightness were also noted.

Tadros et al. (2003) compared 55 historical controls to 55 consecutive patients who were scheduled for coronary angiography with persistent and stable renal insufficiency (a serum creatinine above 106.1 µmol/L or a creatinine clearance below 50 ml/min). The prospective group were given N-Acetylcysteine 600 mg orally, with three doses before angiography and one dose after the diagnostic procedure. Both the historical group and prospective group received 0.45% normal saline or 0.9% normal saline intravenously at 0.5 ml/kg/hr to1.0 ml/kg/hr for 6 to 12 hours prior to and after the procedure. The baseline creatinine (M ± SD) was 176.8 ± 61.9 µmol/L in the prospective group and 159.1 ± 35.4 µmol/L in the historical group, which was the only statistically different characteristics between the two groups ($p = 0.04$). Both ionic and nonionic contrast agents were used in both groups (14/55 versus 8/55 in the prospective group and historical group, respectively; $p = 0.153$), as was the amount of contrast agent (144 ml versus 134 ml in the prospective group and historical group, respectively; $p = 0.5$).

Radiocontrast induced nephropathy was defined as an increase of 25% or more or greater than 44.2 μmol/L in serum creatinine level from baseline at 24 hours and 48 hours. Radiocontrast induced nephropathy was significantly lower in the prospective group, treated with N-Acetylcysteine, 3/55 versus 9/55 in the historical group ($p = 0.02$). The group that received N-Acetylcysteine had a significantly higher baseline serum creatinine ($M \pm SD = 176.8 \pm 61.9$ μmol/L versus 159.1 ± 35.4 μmol/L, $p = 0.04$). Thirty-four out of 55 and 32/55 patients in the N-Acetylcysteine and historical group, respectively, received intravenous 0.9% normal saline with the remaining patients receiving 0.45% normal saline ($p = 0.2$). In a subgroup analysis, patients with a baseline creatinine above 176.8 μmol/L gained more benefit from the N-Acetylcysteine ($p < 0.001$). All patients who developed radiocontrast induced nephropathy were diabetic and hypertensive.

In an Italian article by Vallero et al. (2002), for which an English abstract was attainable, there was no reported benefit to the administration of N-Acetylcysteine 600 mg orally the day before and the day of coronary angiography or angioplasty in 100 consecutive patients with varying degrees of renal function. Both groups received intravenous hydration with hypotonic saline. Of the 100 patients, 20 of them had a creatinine greater than 106.1 μmol/L and the remaining were deemed to have normal renal functioning. The contrast agent used in all cases was iodixanol with a mean volume of 203 ml administered. The definition of nephropathy used was not outlined in the abstract. Among patients with normal renal function, 5.7% in the group who received N-Acetylcysteine and 8.8% in the control group had a rise of serum creatinine concentration above 26.5 μmol/L after 48 hours. In patients with mild renal failure, 16.6% in the N-Acetylcysteine group and none in the control group had a creatinine concentration above

44.2 µmol/L at 48 hours. The conclusion was that there was no potential advantage with the administration of N-Acetylcysteine in the prevention of nephropathy induced by high volumes of contrast agent in patients with normal to mild renal dysfunction.

In the largest prospective, randomized, double-blind, placebo, controlled trial investigating N-Acetylcysteine by Kay et al. (2003) 200 patients with renal insufficiency (a creatinine clearance below 60 ml/min or a serum creatinine above 106.1 µmol/L) who were scheduled for elective coronary angiography with or without percutaneous coronary intervention were assigned to receive N-Acetylcysteine 600 mg orally, twice daily for four doses or placebo starting the day before the procedure. Patients were excluded based on the following criteria: patients on dialysis, acute renal failure, change in use of diuretics or antihypertensive medications, received iodinated contrast media or nephrotoxic drugs within 30 days of the study, overt heart failure, severe valvular disease, or advanced left ventricular dysfunction (ejection fraction less than 35%). All patients received 1 ml/kg/hr of intravenous 0.45% normal saline for 12 hours prior to and 6 hours post contrast exposure. Oral intake of fluid was encouraged except for four hours before the procedure or when clinically contraindicated. All patients received iopamidol, with a mean (± SD) volume of 139 ± 53 ml for all patients. Serum creatinine and urea were measured at 24 hours, 48 hours, and at 7 days following contrast exposure. As well, 24-hour urine creatinine levels were collected at admission, 48 hours and at 7 days. The mean (± SD) baseline serum creatinine and 24-hour creatinine clearance for all patients were 120.2 ± 38.9 µmol/L and 43.5 ± 12.3 ml/min, respectively. The two groups were matched on baseline characteristics, causes of renal impairment, angiographic diagnoses, and clinical course during angiography. In 4% of patients receiving N-Acetylcysteine versus 12% of patients receiving placebo experienced acute contrast-induced renal dysfunction, which was defined as an increase of above 25% in serum creatinine levels (p = 0.03). There was a trend toward a lower incidence of oliguria and acute increase in creatinine levels of at least 50% in the N-Acetylcysteine group. The N-Acetylcysteine group, also had a significant decrease in creatinine concentration from 119.3 μmol/L to 107.9 μmol/L at 48 hours (p < 0.001) than the control group (120.2 μmol/L to 122.0 μmol/L, p =0.13). No patients developed acute nephrotoxicity requiring dialysis.

In a single-center trial by Boccalandro, Amhad, Smalling, and Sdringola (2003) that included patients with a serum creatinine greater than 106.1 μmol/L or a creatinine clearance less than 50 ml/min, who underwent coronary angiography and received more than 1 ml/kg of contrast agent were assessed to determine the effects of prophylactic N-Acetylcysteine. One group received N-Acetylcysteine orally 600 mg twice a day the day before and the day of the procedure, while the control group received nothing. Both groups were hydrated with intravenous 0.45% normal saline at 75 ml/hr for 12 hours before and after the procedure. Serum creatinine was measured at 48 hours. Patients with acute renal failure, end-stage renal disease, taking oral theophylline, mannitol, furosemide, or dopamine, undergoing renal angioplasty or angiography were excluded from the study. All patients received the iso-osmolality nonionic agent iodixanol. The study enrolled 75 patients into the N-Acetylcysteine group and 106 patients into the control group with both groups being matched on baseline characteristics. The volume of contrast agent (M ± SD) used was 192 ± 142 ml in the N-Acetylcysteine group and 191 ± 120 ml in the control group (p = 0.959). The N-Acetylcysteine group had a baseline creatinine (M ± SD) of 159.1 ± 53.0 μmol/L versus 168.0 ± 53.0 μmol/L in the control group (p = 0.95). After 48 hours both groups had a similar mean (± SD) creatinine level of 168.0 ± 70.7 µmol/L versus 176.8 ± 61.9 µmol/L in the N-Acetylcysteine and control group, respectively (p = 0.27). Ten patients had contrast-induced nephropathy in the N-Acetylcysteine group and 13 in the control group (p = 0.84), based on an increase of greater than 44.2 µmol/L in serum creatinine. There were no treatment effects found in a subgroup analysis of patients with poorer renal functioning or those who underwent concomitant percutaneous coronary intervention.

In the prospective, randomized, multi-center controlled study - RAPPID by Baker, Wragg, Kumar, De Palma, Baker, and Knight (2003), 80 patients were investigated to determine the efficacy of intravenous N-Acetylcysteine in inhibiting radiocontrast induced nephropathy in patients undergoing coronary angiography or intervention. Patients with a serum creatinine greater than 123.8 µmol/L or a creatinine clearance less than 50 ml/min were enrolled. These patients were randomly assigned to receive N-Acetylcysteine intravenously at 50 mg/kg in 500 ml of 0.9% normal saline over 30 minutes immediately before contrast exposure with 50 mg/kg in 500 ml of 0.9% normal saline over the subsequent four hours in the treatment arm. In the control arm, intravenous 0.9% normal saline was given at 1 ml/kg/hr for 12 hours before and post procedure. Patients who received nonsteroidal anti-inflammatories within 24 hours of the study, or systolic blood pressure below 90 mmHg, hemodynamically significant valvular heart disease, acute renal failure, or renal failure on dialysis were excluded, as were patients in heart failure. The isotonic, nonionic agent iodixanol was used in all cases with a mean (± SD) volume of 238 ± 155 ml in the treatment group and 222 ± 162 ml in the control group. Angiotensin converting enzyme inhibitors and diuretics were stopped 24 hours before angiography and no patients received nitrates, theophylline, dopamine, furosemide, or mannitol during the study. Serum creatinine was measured before, and at 48 hours, and 96 hours after angiography. The mean (± SD) serum creatinine of this cohort was 159.1 ± 44.2 μmol/L. The control group had an increase (M ± SD) from 154.7 ± 36.2 μmol/L to 160.0 ± 44.2 μmol/L and to 159.1 ± 44.2 μmol/L at 48 hours and 96 hours after contrast (p = 0.99 and 0.23, respectively). The N-Acetylcysteine group had a decrease in the mean (± SD) serum creatinine from 163.5 ± 52.2 μmol/L to 156.5 ± 64.5 μmol/L and 158.2 ± 64.5 μmol/L at 48 hours and 96 hours after contrast (p = 0.02 and 0.023, respectively). Radiocontrast induced nephropathy was defined as an increase in serum creatinine by 25% at 48 hours or 96 hours following contrast exposure. Nephropathy occurred in 10 of the 80 patients, 2 in the N-Acetylcysteine group and 8 in the control group. Out of the 10 patients who developed radiocontrast induced nephropathy, 5 were diabetics. The mean contrast dose given to patients was 253 ml. Adverse events occurred in 10 of the 80 patients, and these events included pulmonary edema and left ventricular failure prior to angiography in which cases the infusions were halted early. Itching, flushing, or transitory rashes were reported in six patients following the initial 30-minute infusion of N-Acetylcysteine. In all six cases symptoms were resolved with the cessation of the infusion.

The studies described above involve the use of N-Acetylcysteine in attempting to decrease the incidence of CIRD in patients who have undergone coronary angiography. All the studies, which were presented and reviewed above, were randomized controlled trials with the exception of the study by Tadros et al. (2003). The patient populations that were investigated were primarily or included those patients undergoing coronary angiography or coronary angioplasty procedures (Table 1).

Based on the 12 studies that have been reviewed in the previous pages the use of N-Acetylcysteine has not been shown to provide an added benefit to the heterogeneous cohorts studied over hydration alone. With the exception of Tepel et al. (2000) study, six of the remaining eleven studies showed statistical significance. But of the six that showed statistical significance, the study by Tadros et al. (2002) was not a randomized control trial and used a historical comparator group. In the study by Tadros et al. the two groups received both ionic and nonionic contrast media with 14/55 in the treatment group and 8/55 in the comparator group receiving nonionic contrast media ($\underline{p} = 0.153$). The use of ionic contrast media is no longer considered standard of care for patients with CIRD.

In the study by Diaz-Sandoval et al. (2002) there was moderate renal dysfunction with the serum creatinine approximately 140 µmol/L with a moderate amount of contrast media volume utilized, approximately 180 ml. In the study by Shyu et al. (2002) the renal dysfunction was severe with a serum creatinine of 246 µmol/L, but a minimal contrast volume of 120 ml. In these two studies the absolute difference in the incidence of CIRD between the treatment and control groups were 37% in the study by Diaz-Sandoval et al. and 21.3% in the study by Shyu et al. with a statistical significance reported to be $\underline{p} = 0.005$ and $\underline{p} = < 0.001$, respectively in support of the use of N-Acetylcysteine. The variations seen between the cohorts are quite discrepant and make comparison of the cohorts difficult to determine the benefits of N-Acetylcysteine.

In the study by Kay et al. (2003) a low risk group was studied with a serum creatinine of 119 µmol/L with a minimal median contrast volume given of 120 ml (mean volume was not reported). The absolute difference in incidence of CIRD was 8% with the higher incidence in the control group (p = 0.03). In the last two studies (Adamian et al., 2002, and Baker et al., 2003) large amounts of contrast volume (iodixanol) were used, approximately 250 ml, with moderate renal dysfunction with a serum creatinine of approximately 160 µmol/L. The absolute difference in the incidence of CIRD was 16% in Baker et al. study and 33.5% in Adamian et al. study (p = 0.045 and p = 0.002, respectively).

In each of these five studies there was a different dosing regimen used to administer the N-Acetylcysteine: (a) oral or intravenous, (b) one dose before and three doses following or twice daily the day before and the day of contrast media exposure, and finally (c) different doses (400m mg or 600 mg orally or150 mg/kg then 50 mg/kg intravenously). These variations between the study protocols, as well as the heterogeneity of the cohorts make the interpretation of the results difficult to compare to the landmark trial by Tepel et al. (2000). It was noted that with the intravenous higher doses of N-Acetylcysteine that side reactions did occur and were most commonly gastrointestinal in nature.

The other five studies that did not show a statistical difference in the use of N-Acetylcysteine in decreasing the incidence of CIRD enrolled patients with moderate to severe renal dysfunction with a serum creatinine range from 132 µmol/L to 202 µmol/L. The incidence of CIRD ranged from 26.3% to as low as 5.7% between these five studies.

Based on two meta-analyses published by Birck, Krzossok, Markowetz, Schnülle, van der Woude, and Braun (2003) and Isenbarger, Kent, and O'Malley (2003) there were 12 studies that were reviewed. Five of these 12 were excluded based on study design, low risk population, and angiographic investigations other than coronary angiography. The incidence of CIRD in the remaining 805 subjects ranged from 8% to 28%, with 8% occurring in the N-Acetylcysteine group and 18% occurring in the control group. There was a relative risk reduction of 56% ($p = 0.02$). With the use of N-Acetylcysteine there was also a significant decrease in serum creatinine, although the absolute improvement in serum creatinine levels were small. Of note some of the trials included in the meta-analyses included the use of other therapies that are experimental in the protection of renal function following angiography (i.e., fenoldopam).

Table 1

Study Characteristics and Results of Trials With the Use of N-Acetylcysteine in Decreasing the Incidence of CIRD*

Investigator (Date)	Tepel et al. (2000)	Diaz-Sandoval et al. (2002)	Briguori et al. (2002)	Shyu et al. (2002)
Population Size	83	54	183	121
Type of Diagnostic Investigation	Elective Computed Tomography	Elective Coronary Angiography	Elective Coronary and Peripheral Angiography ± Angioplasty	Elective Coronary Angiography ± Angioplasty
Baseline Serum Creatinine (µmol/L, M ± SD)	220.0 ± 114.4 - NAC** 211.2 ± 114.4 - Control	146.1 ± 5.3 - NAC 137.3 ± 4.4 - Control	132. ± 37.8 - NAC 135.5 ± 31.7 - Control	246.4 ± 70.4 - NAC 246.4 ± 70.4 - Control
Diabetics/Group (%)	32 - NAC vs 33 - Control	48 - NAC vs 52 - Control	43 - NAC vs 32.5 - Control	63 - NAC vs 64 - Control
Volume of Contrast Media (ml, M ± SD)	75 in both groups	189 ± 12 - NAC vs 179 ± 8 - Control	194 ± 127 - NAC vs 200 ± 144 - Control	119 ± 3 - NAC vs 115 ± 48 - Control
Type of Contrast	Iopromide	Ioxilan	Iopromide	Iopamidol
Regimen of NAC	600 mg orally 2x daily the day before and day of procedure X 4 doses (total)	600 mg orally 1 dose before and 3 doses after the procedure X 4 doses (total)	600 mg orally 2x daily the day before and day of procedure X 4 doses (total)	400 mg orally 2x daily the day before and day of procedure X 4 doses (total)
Regimen of Hydration	0.45% S◆ at 1 ml/kg/hr for 12 hours pre and 12 hours post angiography	0.45% S at 1 ml/kg/hr for 2 - 12 hours pre and 12 hours post angiography	0.45% S at 1 ml/kg/hr for 12 hours pre and 12 hours post angiography	0.45% S at 1 ml/kg/hr for 12 hours pre and 12 hours post angiography
Definition of CIRD (Increase in Serum Creatinine)	Increase ≥ 44 µmol/L within 48 hours	Increase ≥ 44 µmol/L or by 25% within 48 hours	Increase by 25% within 48 hours or need for dialysis	Increase ≥ 44 µmol/L within 48 hours
Incidence of CIRD/Group (%, p)	2 - NAC vs 21- Control (p = 0.01)	8 - NAC vs 45 - Control (p = 0.005)	6.5 - NAC vs 11 - Control (p = 0.22)	3.3 - NAC vs 24.6 - Control (p < 0.001)

* CIRD = Contrast-Induced Renal Dysfunction.

** NAC = N-Acetylcysteine.

◆ S = Normal Saline.

❖ NS = Not Significant.

Table 1 (continued)

Study Characteristics and Results of Trials With the Use of N-Acetylcysteine in Decreasing the Incidence of CIRD*

Investigator (Date)	Durham et al. (2002)	Adamian et al. (2002)	Oldemeyer et al. (2002)	Tadros et al. (2002)
Population Size	79	57	96	110
Type of Diagnostic Investigation	Elective Coronary Angiography ± Angioplasty	Elective Coronary Angiography + Angioplasty	Elective Coronary Angiography ± Angioplasty	Elective Coronary Angiography
Baseline Serum Creatinine (μmol/L, M ± SD)	193.6 ± 35.2 - NAC** 202.4 ± 44.0 - Control	166.3 ± 35. 2 - NAC 172.5 ± 44.0 - Control	143.4. ± 71.3 - NAC 146.1 ± 57.2 - Control	176.0 ± 61.6 - NAC vs 158.4 ± 35.2 - Historical (Hx) Control
Diabetics/Group (%)	50 - NAC vs 46.3 - Control	57 - NAC vs 70 - Control	41 - NAC vs 49 - Control	54.6 - NAC vs 27.3 - Control
Volume of Contrast Media (ml, M ± SD)	77.4 ± 35.9 - NAC vs 84.7 ± 42.1 - Control	273 ± 113 - NAC vs 303 ± 152 - Control	134 ± 171 - NAC vs 127 ± 73 - Control	143.9 ± 82.9 - NAC vs 134.3 ± 79.7 Hx Control
Type of Contrast	Iohexol (Nonionic)	Iodixanol (Nonionic)	Iopamidol	Ionic vs Nonionic
Regimen of NAC	1200 mg orally 1 hour before and 3 hours after the procedure X 2 doses (total)	600 mg orally 2x daily	1500 mg orally 2x daily the day before and day of procedure X 4 doses (total)	600 mg orally 3 doses before and 1 dose after the procedure X 4 doses (total)
Regimen of Hydration	0.45% S◆ at 1 ml/kg/hr for up to 12 hours pre and up to 12 hours post angiography	Intravenous hydration - no details given	0.45% S at 1 ml/kg/hr for 12 hours pre and 12 hours post angiography	0.45% or 0.9% S at 0.5 - 1 ml/kg/hr for 6 - 12 hours pre and post angiography
Definition of CIRD (Increase in Serum Creatinine)	Increase ≥ 44 μmol/L within 48 hours	Increase by 25% within 48 hours	Increase by 25% within 48 hours	Increase ≥ 44 μmol/L or by 25% within 48 hours
Incidence of CIRD/Group (%, p)	26.3 - NAC vs 22.0 - Control (p = NS❖)	2.9 - NAC vs 36.4 - Control (p = 0.002)	8.2 - NAC vs 6.4 - Control (p = 0.74)	5 - NAC vs 16 - Hx Control (p = 0.02)

* CIRD = Contrast-Induced Renal Dysfunction.

** NAC = N-Acetylcysteine.

◆ S = Normal Saline.

❖ NS = Not Significant.

Table 1 (continued)

Study Characteristics and Results of Trials With the Use of N-Acetylcysteine in Decreasing the Incidence of CIRD*

Investigator (Date)	Vallero et al. (2002)	Kay et al. (2003)	Boccalandro et al. (2003)	Baker et al. (2003)
Population Size	100	200	181	80
Type of Diagnostic Investigation	Elective Coronary Angiography ± Angioplasty	Elective Coronary Angiography	Elective Coronary and Peripheral Angiography ± Angioplasty	Elective Coronary Angiography ± Angioplasty
Baseline Serum Creatinine (μmol/L, M ± SD)	Not given	119.7 ± 35.2 – NAC** 118.8 ± 35.2 - Control	159.1 ± 53.0 - NAC 168.0 ± 53.0 - Control	163.5 ± 51.9 - NAC 154.7 ± 36.2 - Control
Diabetics/Group (%)	Not given	39 - NAC vs 36 - Control	67 - NAC vs 57 - Control	41 - NAC vs 44 - Control
Volume of Contrast Media (ml, M ± SD)	203 (no SD available)	120 (median) - NAC vs 130 (median) - Control	192 ± 142 - NAC vs 191 ± 120 - Control	238 ± 155 - NAC vs 222 ± 162 - Control
Type of Contrast	Iodixanol (Nonionic)	Iopamidol	Iodixanol (Nonionic)	Iodixanol (Nonionic)
Regimen of NAC	600 mg orally twice daily the day before and the day of procedure X 4 doses (total)	600 mg orally twice daily the day before and the day of procedure X 4 doses (total)	600 mg orally twice daily the day before and the day of procedure X 4 doses (total)	IV 150mg/kg/500 S pre and 50mg/kg/500 S post angiography
Regimen of Hydration	Hypotonic solution - no details given	0.45% S◆ at 1 ml/kg/hr for 12 hours pre and 6 hours post angiography	0.45% S at 75 ml/hr for 12 hours pre and 12 hours post angiography	S at 1 ml/kg/hr for 12 hours pre and post angiography Control
Definition of CIRD (Increase in Serum Creatinine)	Increase > 44 μmol/L within 48 hours	Increase by 25% within 48 hours	Increase > 44 μmol/L within 48 hours	Increase by 25% within 48 to 96 hours
Incidence of CIRD/Group (%, p)	5.7 - NAC vs 8.8 - Control (p = NS❖)	4 - NAC vs 12 - Control (p = 0.03)	13 - NAC vs 12 - Control (p = 0.84)	5 - NAC vs 21 - Control (p = 0.045)

* CIRD = Contrast-Induced Renal Dysfunction.

** NAC = N-Acetylcysteine.

◆ S = Normal Saline.

❖ NS = Not Significant.

CHAPTER THREE

Method

The purpose of this study was to determine the efficacy of N-Acetylcysteine in preventing the incidence of contrast-induced renal dysfunction (CIRD) in patients who were admitted to the Royal Alexandra Hospital with an acute coronary syndrome (ACS), had biochemical evidence of renal dysfunction, and were scheduled for risk stratification through coronary angiography.

Design

A prospective, double-blind, randomized, placebo, controlled trial was used to assess the efficacy of oral N-Acetylcysteine and intravenous hydration in decreasing the incidence of CIRD in patients admitted with an ACS and renal dysfunction who underwent risk stratification with coronary angiography with or without concomitant percutaneous coronary intervention (PCI) at the Royal Alexandra Hospital between April, 2003 to February, 2004.

Patients were randomized to two groups:

1. *Treatment Group* – Patients received intravenous hydration of 0.45% normal saline at 1 ml/kg/hr 4 hours to 6 hours before and 12 hours after coronary angiography with or without concomitant PCI and 600 mg orally of N-Acetylcysteine, for a total of four doses, with the first dose at 0800 the day of the procedure and three doses after coronary angiography with or without concomitant PCI at intervals of twice a day with the first dose dose post-angiography at 2000.

2. *Control Group* – Patients received intravenous hydration of 0.45% normal saline at 1 ml/kg/hr 4 hours to 6 hours before and 12 hours after coronary angiography with or without concomitant PCI and placebo orally, for a total of four doses, with the first dose at 0800 the day of the procedure and three doses after coronary angiography with or without concomitant PCI at intervals of twice a day with the first dose post-angiography at 2000.

The primary outcome measures of renal function to determine CIRD were serum creatinine and creatinine clearance (calculated by applying the Cockcroft-Gault formula to serum creatinine: Creatinine clearance [CrCl] = 140-age [years] x ideal body weight [kg]/serum creatinine [μmol/L]; with adjustments for male gender calculated by: $CrCl_{male} = CrCl \times 1.2$). These outcome measures were assessed on admission, the morning of coronary angiography, and then at 24 hours, and 48 hours after coronary angiography (Figure 1). As well, patient's clinical presentation profiles were reviewed and examined to determine associated risk factors for CIRD in this cohort such as age, gender, recorded peak creatine kinase (CK), Troponin I, Killip or New York Heart Association (NYHA) class, and the presence of diabetes mellitus.

Sample

Patients admitted to the Royal Alexandra Hospital, with a diagnosis of an ACS were eligible for inclusion in the study. The additional inclusion criteria were:

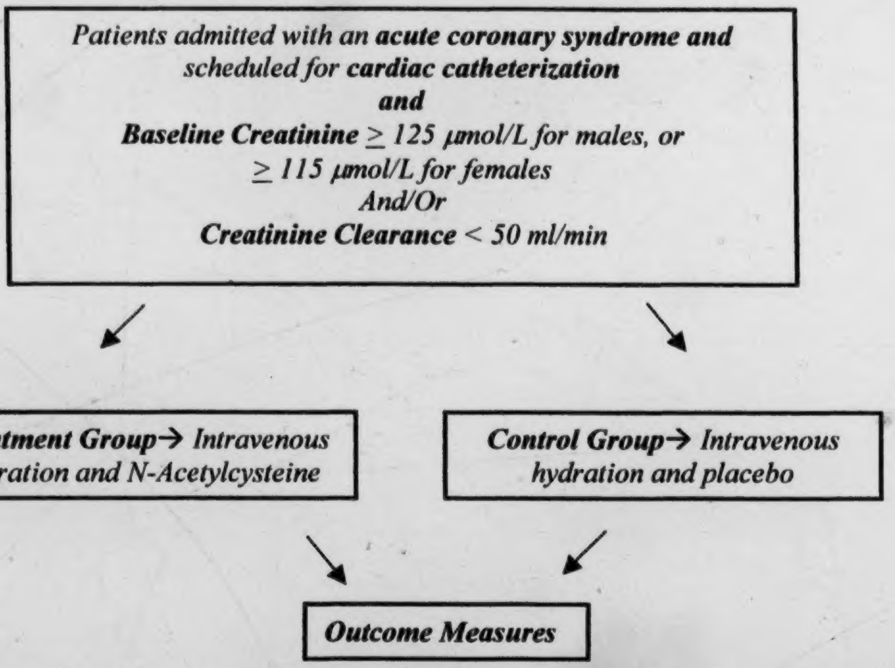
- ☐ Age equal to or greater than 18 years
- ☐ Scheduled for coronary angiography with or without concomitant PCI
- ☐ Baseline creatinine equal to or greater than 125 μmol/L for males, or equal to or greater than 115 μmol/L for females; and/or creatinine clearance below 50 ml/min

- Diagnosed with an ACS with or without electrographic changes; and/or quantitative biochemical markers as measured by CK, Creatine Kinase-myocardial cell isoenzyme (CK-MB) (above 10 U/L), Ratio (above 10%), and/or Troponin I (above 0.15 μg/L)
- Able to provide informed consent and available for follow-up.

The exclusion criteria were:

- Hemodynamic instability (systolic blood pressure below 90 mmHg) requiring inotropic support
- Pregnant
- Acute gastrointestinal disorder (unable to tolerate oral medication)
- Killip class III or IV, NYHA III or IV or patient deemed by the Cardiologist unsuitable to receive intravenous hydration therapy
- Known sensitivity to N-Acetylcysteine (based on patient history or knowledge)
- Current treatment with theophylline or mannitol
- Dialysis therapy
- Participation in another study or use of experimental drug.

The sample size for this study was projected to be 130 patients, with 65 randomized to the treatment group and 65 randomized to the control group. Based on an absolute difference in the incidence of CIRD of 17% and a two-tailed alpha of 0.05, the calculated power of this study was 0.80.


Patients admitted with an acute coronary syndrome and scheduled for cardiac catheterization
and
Baseline Creatinine ≥ 125 µmol/L for males, or ≥ 115 µmol/L for females
And/Or
Creatinine Clearance < 50 ml/min
Treatment Group→ Intravenous hydration and N-Acetylcysteine
Control Group→ Intravenous hydration and placebo
Outcome Measures

Measures	Time of Enrolment	Morning of Angio◆	24 hours Post-Angio	48 hours Post-Angio
CK*◆	X	X	–	–
CK-MB/Ratio**❖	X	X	–	–
Troponin I❖	X	X	–	–
C-Reactive Protein (High Sensitivity)	X	–	–	–
Serum Creatinine	X	X	X	X
Creatinine Clearance	X	X	X	X

* CK = Creatine Kinase.

** CK-MB = Creatine Kinase- myocardial cell isoenzyme.

◆ measured until peak concentration obtained.

❖ measured until positive or CK-MB/Ratio showed infarct pattern.

◆ Angio = Angiography.

Figure 1. Study Design

Definition of Terms

Acute Coronary Syndrome *(ACS)* – A constellation of clinical symptoms that are compatible with AMI; and is usually caused by the disruption of an atherosclerotic plaque in the coronary artery resulting in activation of the coagulation cascade and subsequent partial or complete occlusion of the vessel. Acute coronary syndromes encompass AMI, both ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA). NSTEMI differs from UA in that there is evidence of myocardial necrosis detected by biochemical markers (CK, CK-MB, and Troponin I). Changes to the electrocardiogram (EKG), either ST depression or T wave changes, may be present with either condition, but tend to be transient with UA, and may not persist with NSTEMI (Braunwald et al., 2002).

Renal Dysfunction – Serum creatinine equal to or greater than 125 μmol/L for males, or equal to or greater than 115 μmol/L for females; and/or creatinine clearance below 50 ml/min on admission laboratory testing.

Contrast-Induced Renal Dysfunction *(CIRD)* – An absolute increase in serum creatinine of or greater than 44 μmol/L, and/or a relative increase of above 25% above baseline within 48 hours after contrast media exposure.

N-Acetylcysteine – A thiol-compound and is an acetylated variant of the amino acid L-cysteine and has historically been used as a mucolytic agent in a variety of respiratory illnesses. With a molecular weight of 163.2 and a chemical formula of $C_5H_9NO_3S$, N-Acetylcysteine is an excellent source of sulfhydryl (SH) groups. It is the abundance of SH groups which are theorized to largely be responsible for a great deal of the metabolic activity of N-Acetylcysteine (Kelly, 1998). This thiol-compound that is rapidly absorbed following oral dosing, undergoes extensive first pass metabolism by cells of the small intestine and liver. Only a small percentage of intact N-Acetylcysteine molecules arrives in the plasma and subsequently in the tissue. Peak concentration typically appears in the plasma in less than one hour following oral administration (Kelly, 1998). The plasma half-life of free N-Acetylcysteine is estimated to be about 2.15 hours with virtually no N-Acetylcysteine detectable at 10 hours to 12 hours post administration (Kelly, 1998). The bioavailability is 6% to 10%, with the amount excreted unchanged in the urine within 24 hours between 13% to 38%, and the volume of distribution ranging from 0.33 L/kg to 0.47 L/kg. N-Acetylcysteine has no active metabolites.

The beneficial effects of orally administered N-Acetylcysteine are largely theorized and are attributed to N-Acetylcysteine's ability to either reduce extracellular cystine to cysteine, or to be a source of SH metabolites. The increase in availability of SH groups from N-Acetylcysteine can stimulate glutathione (GSH) synthesis by enhancing glutathione-S-transferase activity which is theorized to improve endothelium-dependent vasomotion and scavenge oxygen-derived free radicals (Kelly, 1998; Shyu et al., 2002). N-Acetylcysteine is also thought to promote detoxification by increasing the expression of nitric oxide synthase which can improve blood flow, to act directly on reactive oxidant radicals, thus reducing the ability of generated oxygen free radicals to damage cells, and to inhibit cell apoptosis (Kelly, 1998; Shyu et al., 2002).

The majority of documented adverse reactions to N-Acetylcysteine are case reports in the treatment of acetaminophen poisoning. The rare side effects cited were urticaria, pruritis, flushing, edema of the face and lips, bronchospasm, asthma, respiratory depression, tachycardia, hypotension, hemolysis, 'cardiovascular collapse' (Gervals, Lussier-Labelle, & Beaudet, 1984; Mant, Tempowski, & Talbot, 1984; Sunman, Hughes, & Sever, 1992; Vale & Wheeler, 1982), nausea, vomiting, and dizziness (Walton, Mann, & Shaw, 1979). One case report cited increased intracranial pressure as a side effect secondary to mucolytic therapy of inhaled N-Acetylcysteine (Venturelli & Tein, 1984). Another side effect observed by Oikawa, Yamada, Yamashita, Tada-Oikawa, and Kawanishi (1999) was that N-Acetylcysteine could induce metal-dependent hydrogen peroxide (H_20_2) generation that could lead to cellular and isolated DNA mutations, and therefore possibly have both carcinogenic and anti-carcinogenic effects (Oikawa et al., 1999). However, further investigations are necessary on the safety and carcinogenic risk assessment of N-Acetylcysteine (Oikawa et al., 1999).

Data Collection Protocol

Patients who presented to the Royal Alexandra Hospital and were admitted either to Patient Care Unit 24 or the Coronary Care Unit with a history compatible with an ACS with or without EKG changes were assessed for positive biochemical marker evidence of myocardial necrosis during their hospital stay according to clinical presentation (i.e., at the time of admission or if there were recurrent symptoms compatible with an ACS during admission). The patient's renal functioning was assessed, based on gender specific serum creatinine levels; and/or creatinine clearance (calculated by applying the Cockcroft-Gault formula to serum creatinine: Creatinine clearance [CrCl] = 140-age [years] x ideal body weight [kg]/serum creatinine [µmol/L]; with adjustments for male gender calculated by: $CrCl_{male}$ = CrCl x 1.2) at the time of admission.

Those patients who had both evidence of an ACS and renal dysfunction, and were scheduled to undergo risk stratification with coronary angiography with or without concomitant PCI were approached by the principal investigator; and were given the Information Sheets (Appendix A) to review, and an oral explanation was provided of the rational behind the investigation and the study protocol. An opportunity was given to each patient to review, discuss, and ask questions about the study with family members and the principal investigator, except in one case in which the Cardiology Research Nurse obtained consent.

After questions were clarified and verbal consent was received, the Consent Form (Appendix B) was signed by the study subject with the principal investigator as the witness in all cases, except the afore mentioned single study subject. A copy of the consent was provided for the study subject. The attending Cardiologist and the family doctor, if the subject had one, were informed of the subject's enrolment into the study. All orders regarding enrolment, laboratory assays, and study treatment protocols were written and reviewed with the bedside nurse or nurse in charge.

The study subject's inclusion and exclusion criteria were assessed and recorded as per the Enrolment Criteria form (Appendix C). Those participants who were enrolled in the study went on to have further evaluation of their renal function with a random urine taken at the time of enrolment for urinalysis and microalbuminuria; and had their cardiac evaluation further defined by the measurement of the high sensitivity C-Reactive Protein, an inflammatory marker drawn at the time of enrolment. Serum creatinine was measured and recorded at the time of admission, the morning of coronary angiography, and then at 24 hours, and 48 hours after coronary angiography. The creatinine clearance was calculated using the Cockcroft-Gault formula and recorded at the same intervals as serum creatinine as per the Data Collection Tool (Appendix D). If there was a rise in serum creatinine and/or decline in creatinine clearance, blood work to determine renal function was drawn on a daily basis until it returned to baseline or stabilized, as deemed by the Cardiologist. The participant's clinical presentation profile and serial biochemical markers were also recorded as per the Data Collection Tool (Appendix D), and other information such as urgency of catheterization, coronary anatomy, the type and quantity of contrast dye used, as well as the CK peak were recorded to correlate to the incidence of CIRD in this cohort.

With the assistance of the Pharmacy Department, the mixing of N-Acetylcysteine was tested based on odour tests. It was found that a minimum volume of 27 ml of Coca-Cola was sufficient to mask the odour. No taste tests were conducted. The N-Acetylcysteine was mixed in 27 ml of Coca-Cola (total volume of 30 ml) for each dose and sent to the unit and given to the patient within an hour of mixing. The placebo was 30 ml of Coca-Cola and was dispensed similarly. The N-Acetylcysteine or placebo was administered in a twice a day dosing regimen with one dose before and three doses following coronary angiography. The nurse who was assigned to the patient administered the medication/placebo.

Study subjects who agreed to participate in this study were randomized by the Pharmacy Department at Royal Alexandra Hospital to maintain double-blinding by drawing from a pile of consent packages that had been randomly shuffled (simple randomization) to receive either four doses of N-Acetylcysteine and intravenous hydration of 0.45% normal saline at a rate of 1 ml/kg/hr for 4 hours to 6 hours before and 12 hours following coronary angiography with or without concomitant PCI (Treatment

Group), or placebo in a similar dosing regimen and similar intravenous hydration (Control Group).

Data Analysis

Descriptive statistics (mean, median, standard deviation, range, and percentages) were used for analysis of sample characteristics and each variable of the study. The baseline characteristics of the Treatment and Control Groups were compared using Chi-square (Fisher's Exact Test) for categorical data or t-test analysis for continuous data. The incidence of CIRD in the Treatment Group compared to the Control Group was analyzed using Chi-square. A repeated measures analysis of variance (ANOVA) was done to examine the change in serum creatinine and the calculated creatinine clearance from enrolment, to baseline, to 24 hours, to 48 hours, as well between the Treatment Group and the Control Group. The level of significance was $\underline{p} < 0.05$.

Ethical Considerations

Ethical approval was obtained from the Health Research Ethics Board (Panel A), Capital Health. As well, support from the Medical Officer and the Patient Care Manager of the Coronary Care Unit, Royal Alexandra Hospital were obtained for the implementation of this study.

Several strategies were utilized to protect the rights of the study patients who agreed to participate in the study. First, the study was explained, both verbally and written via an Information Sheets (Appendix A), and signed consent was obtained with the use of the Consent Form (Appendix B). The study subject was informed of the purpose of the study, that their participation was voluntary, and that they were permitted to withdraw at any time with no consequences to the medical or nursing care they were provided or received.

There were no additional physical risks to the patient for participating in this study, nor could there be any assured benefits gained by participating in this study. The potential side effects included urticaria, pruritis, flushing, edema of the face and lips, bronchospasm, asthma, respiratory depression, tachycardia, hypotension, hemolysis, 'cardiovascular collapse' (Gervals, Lussier-Labelle, & Beaudet, 1984; Mant, Tempowski, & Talbot, 1984; Sunman, Hughes, & Sever, 1992; Vale & Wheeler, 1982), nausea, vomiting, dizziness, (Walton, Mann, & Shaw, 1979) and increased intracranial pressure (Venturelli & Tein, 1984). These were reviewed with the study participants and explained that they were rare and have been seen with the use of this medication in larger and intravenous doses unlike what was being administered in this study. Each study subject was assured that if any signs or symptoms of an adverse reaction were noted, the condition would be assessed and the study subject would be treated appropriately and withdrawn from the study with no disruption to the care they received. Confidentiality of the participant was maintained, and no names were attached to data collection forms. A coded numbering system ensured confidentiality. The participant's names, code numbers, and data are on separate sheets, which are kept in a separate locked filing cabinet.

CHAPTER FOUR

Findings

To determine the efficacy of N-Acetylcysteine in decreasing the incidence of contrast-induced renal dysfunction (CIRD), a prospective, double-blind, randomized, placebo, controlled, study was conducted at the Royal Alexandra Hospital. The study enrolled patients admitted with an acute coronary syndrome with or without evidence of myocardial ischemia, who were scheduled for coronary angiography with or without concomitant percutaneous coronary intervention (PCI), who had a creatinine clearance of less than 50 ml/min and/or a serum creatinine equal to or greater than 125 μmol/L in males, or equal to or greater than 115 μmol/L in females prior to coronary angiography. Those patients who consented to participate in the study were randomized by the Pharmacy Department into one of two groups: (a) patients received intravenous hydration of 0.45% normal saline at 1 ml/kg/hr 4 hours to 6 hours before and 12 hours after coronary angiography with or without concomitant PCI and 600 mg orally of N-Acetylcysteine, for a total of four doses (Treatment Group), or (b) patients received intravenous hydration of 0.45% normal saline at 1 ml/kg/hr 4 hours to 6 hours before and 12 hours after coronary angiography with or without concomitant PCI and placebo orally, for a total of four doses (Control Group).

All data were entered into the Statistical Package for the Social Sciences-Version 11.0 for Windows. Descriptive statistics (mean, median, standard deviation, range, percentages) were used for analysis of sample characteristics and each variable of the study. The baseline characteristics of the Treatment and Control Groups were compared using Chi-square (Fisher's Exact Test) or t-test analysis. The incidence of CIRD in the

Treatment Group compared to the Control Group was analyzed using Chi-square (Fisher's Exact Test). A repeated measures analysis of variance (ANOVA) was done to examine the change in serum creatinine and the calculated creatinine clearance from enrolment, to baseline, to 24 hours, and to 48 hours, as well as between the Treatment Group and the Control Group.

Screening and Final Study Cohort

From April, 2003 to February, 2004, 132 patients were screened for possible enrolment into the study (Figure 2). Of the patients screened, 19 patients were excluded based on heart failure, 19 patients were risk stratified using methods other than coronary angiography, 18 patients declined participation, 17 patients underwent primary angiography, five patients were enrolled in another investigation at the time of screening, and five patients had a diagnosis of either dementia, inebriation, or encephalopathy, and were unable to give informed consent, four patients were unable to read or write English, three patients were ordered to have the N-Acetylcysteine and intravenous hydration by the attending Cardiologist based on a perceived increase in risk, and two patients were on dialysis at the time of admission.

For the participants who were enrolled in the study, their hospital course was followed until discharge from Cardiology. The morning of coronary angiography each of the participants were assessed once again for exclusion criteria; if the participant still fulfilled all the inclusion criteria, the Pharmacy Department was notified to randomize the study subject and dispense the study drug. Of those randomized, one patient acutely began to have chest pain and became relatively hypotensive after randomization was

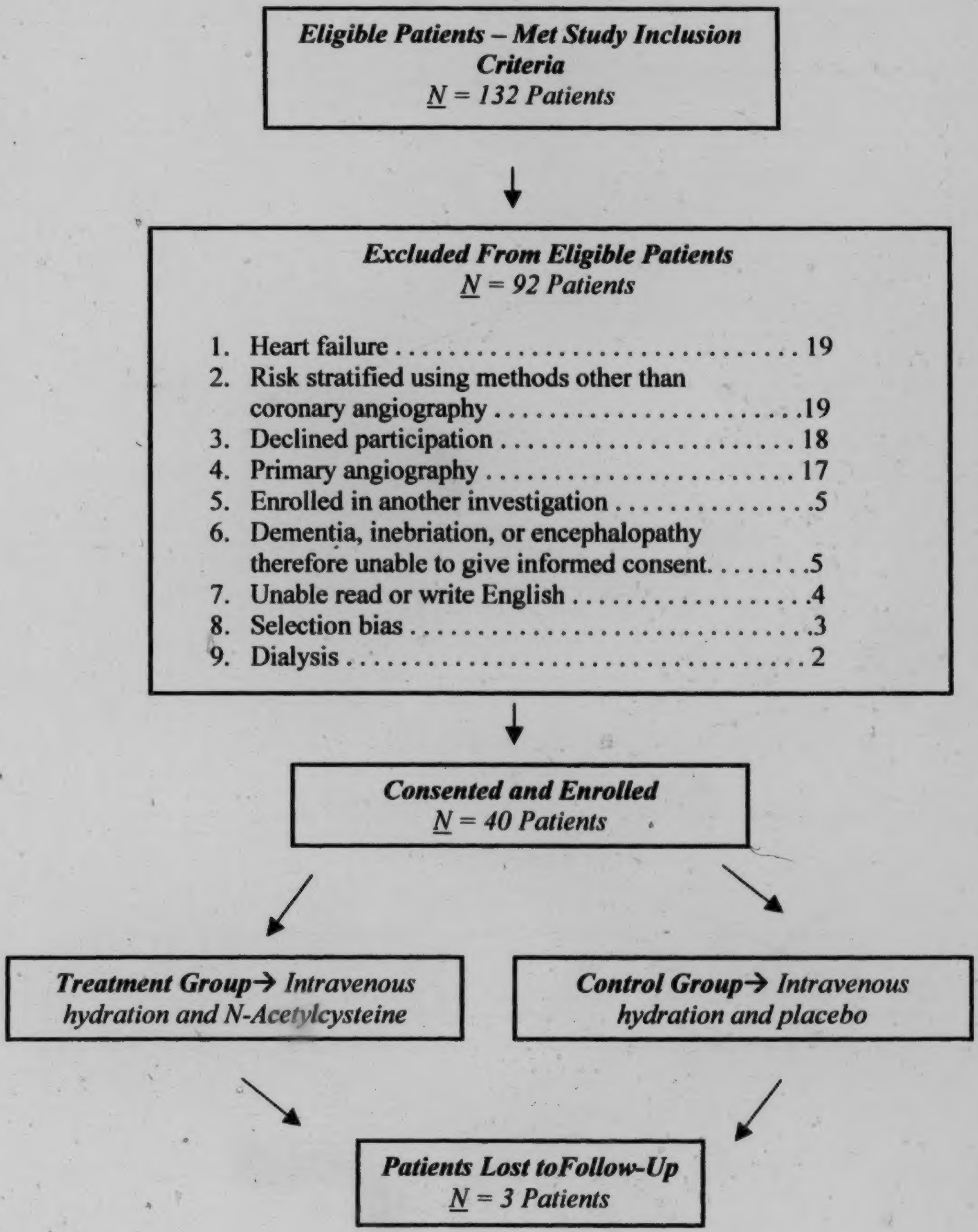

Eligible Patients – Met Study Inclusion Criteria
N = 132 Patients
Excluded From Eligible Patients
N = 92 Patients
1. Heart failure 19
2. Risk stratified using methods other than coronary angiography 19
3. Declined participation 18
4. Primary angiography 17
5. Enrolled in another investigation 5
6. Dementia, inebriation, or encephalopathy therefore unable to give informed consent. 5
7. Unable read or write English 4
8. Selection bias 3
9. Dialysis 2
Consented and Enrolled
N = 40 Patients
Treatment Group→ Intravenous hydration and N-Acetylcysteine
Control Group→ Intravenous hydration and placebo
Patients Lost toFollow-Up
N = 3 Patients

Figure 2. Study Recruitment and Enrolment

completed and the study drug dispensed. The patient, subsequently, went urgently to the cardiac catheterization laboratory, but was deemed appropriate to continue to receive hydration and the study drug. This patient received four hours of hydration prior to catheterization. A second patient had stuttering chest pain, which became persistent following randomization. The patient met none of the exclusion criteria, in terms of heart failure, or hypotension requiring inotropic support, thus continued in the study, but received four hours of hydration prior to going to the cardiac catheterization laboratory urgently. A third patient had persistent electrocardiographic changes and was assessed and subsequently underwent urgent cardiac catheterization, and also received four hours of prehydration. With both these patients the study drug was given within 1½ hours of contrast media exposure. None of these three patients developed CIRD. Finally, there were three patients who did not receive the final dose of the study drug because of being discharged.

Characteristics of the Study Cohort

Demographics of the Cohort

Forty patients made up the final cohort with 20 patients in the Treatment Group and 20 patients in the Control Group. The study groups were matched on clinical characteristics at baseline (Table 2). The age ranged from 39 years to 87 years, with a mean (± SD) age of 76.4 ± 5.9 years in the Treatment Group and 74.7 ± 9.7 years in the Control Group. The subjects were overweight with a body mass index (M ± SD) of 28.55 ± 6.04 kg/m^2 in the Treatment Group and 27.55 ± 4.62 kg/m^2 in the Control Group. As well, the Treatment Group and the Control Group were similar on the cardiac risk factors of smoking (10 [50%] versus 11 [55%], respectively), hypertension (11 [55%] versus 12

[60%], respectively), known coronary artery disease (10 [50%] versus 9 [45%], respectively), previous myocardial infarction (10 [50%] versus 8 [40%], respectively), dyslipidemia (10 [50%] versus 14 [70%], respectively), and diabetes mellitus (8 [40%] in both groups), and congestive heart failure (6 [30%] in both groups). Only one patient in the Control Group had a Killip and New York Heart Association class of greater than II. This patient was the same patient who decompensated but continued with the study protocol. Also, one patient in the Control Group had an identified risk factor for CIRD of multiple myeloma; however, this patient did not develop CIRD.

All patients enrolled in the study had a diagnosis of an acute coronary syndrome; 55% had high risk unstable angina (25% [n = 5] in the Treatment Group versus 30% [n = 6] in the Control Group), 25% had low risk unstable angina (10% [n = 2] in the Treatment Group versus 15% [n = 3] in the Control Group), 90% had a non-ST elevation myocardial infarction (45% [n = 9] in each group), and 30% had a ST elevation myocardial infarction (20% [n = 4] versus 10% [n = 2] in the Treatment Group and in the Control Group, respectively).

Medication Profile on Admission of the Cohort

The medication profile of patients (Table 3) was reviewed to assess for the presence of nephrotoxic or potentially nephrotoxic drug usage prior to admission. A total of 11 patients (8 [40%] in the Treatment Group and 3 [15%] in the Control Group) were taking potentially nephrotoxic drugs. Four patients were taking nonsteroidal anti-inflammatories (either Vioxx or Celebrex), 5 patients were taking aldactone, one patient

Table 2

Clinical Characteristics of the Study Cohort

Characteristics	**Treatment Group (n = 20)**	**Control Group (n = 20)**	**p value**
Age (years, M ± SD)	76.4 ± 5.9	74.7 ± 9.7	0.506
Gender (Male/Female, n [%])	12/8 (60/40)	14/6 (70/30)	0.741
Body Mass Index (kg/m^2, M ± SD)	28.55 ± 6.04	27.55 ± 4.62	0.560
Smoker (current + former, n [%])	10 (50)	11 (55)	–
Hypertension (n [%])	11 (55)	12 (60)	1.0
Diabetes Mellitus (n [%])	8 (40)	8 (40)	1.0
Known Coronary Artery Disease (n [%])	10 (50)	9 (45)	1.0
Previous Myocardial Infarction (n [%])	10 (50)	8 (40)	0.751
Dyslipidemia (n [%])	10 (50)	14 (70)	0.333
History of Congestive Heart Failure (n [%])	6 (30)	6 (30)	1.0
Killip Class (III/IV, n [%])	–	1 (5)	–
New York Heart Association (III/IV, n [%])	–	1 (5)	–
Other Risk Factors for CIRD* (n [%])	–	1 (5)	1.0
Admission Diagnosis (n [%])			
Unstable Angina-High Risk	5 (25)	6 (30)	–
Unstable Angina-Low Risk	2 (10)	3 (15)	–
NSTEMI**	9 (45)	9 (45)	–
STEMI◆	4 (20)	2 (10)	–

* CIRD = Contrast-Induced Renal Dysfunction.

** NSTEMI = Non-ST Elevation Myocardial Infarction.

◆ STEMI = ST Elevation Myocardial Infarction.

was taking metalazone, and one patient was taking muocmyst 20% via inhalation. Both groups had an equal number of subjects who were taking aspirin (40%), angiotensin converting enzyme inhibitor (45%), angiotensin receptor blocker (25%), calcium channel blocker (25%), and digoxin (10%). In the Treatment Group, 10 patients (50%) were taking β-blocker therapy compared to 8 patients (40%) in the Control Group (p = 0.751). The Control Group had 7 patients (35%) versus 3 patients (15%) in the Treatment Group (p = 0.273), who were on anticoagulant/antiplatelet therapy, which included warfarin, or thienopyridine therapies. Twice as many patients in the Treatment Group were on diuretics (10 versus 5, p = 0.191).

Table 3

Medication Profile of the Study Cohort on Hospital Admission

Medication Classes (n [%])	**Treatment Group (n = 20)**	**Control Group (n = 20)**	**p value**
ASA	8 (40)	8 (40)	1.0
Anticoagulant/Antiplatelet	3 (15)	7 (35)	0.273
β-Blocker	10 (50)	8 (40)	0.751
Angiotensin Converting Enzyme Inhibitor	9 (45)	9 (45)	1.0
Angiotensin Receptor Blocker	5 (25)	5 (25)	1.0
Calcium Channel Blocker	5 (25)	5 (25)	1.0
Diuretic	10 (50)	5 (25)	0.191
Digoxin	2 (10)	2 (10)	1.0
Lipid Lowering Therapy	6 (30)	10 (50)	0.333
Other	8 (40)	3 (15)	0.155

Medications Initiated at the Time of Hospital Admission of the Cohort

All patients were admitted with varying degrees of an acute coronary syndrome and were subsequently placed on appropriate therapies (Table 4). There were no statistically significant differences noted between the groups based on the medications initiated at the time of admission. Ten versus 11 patients (50% versus 55%), in the Treatment Group and in the Control Group, respectively (p = 1.0) were placed on aspirin therapy. Unfractionated heparin was initiated for 12 patients (60%) in the Treatment Group and 11 patients (55%) in the Control Group (p = 1.0); while 6 (30%) versus 8 (40%) patients in the Treatment Group and in the Control Group, respectively, received low molecular weight heparin therapy.

There were more patients in the Control Group than in the Treatment Group (9 [45%] compared to 5 [25%], $p = 0.320$) who were initiated on β-blocker therapy at the time of admission. In each of the two groups there were equal numbers initiated on angiotensin converting enzyme inhibitor 7 (35%), lipid lowering therapy 5 (25%), glycoprotein IIb/IIIa inhibition 1 (5%), and one (5%) in each group was initiated on other medications, which included aldactone and amiodarone ($p = 1.0$). Thienopyridine therapy was started in 6 (30%) versus 7 (35%) of study patients in the Treatment and Control Group, respectively. There was twice the usage of diuretics and thrombolytics in the Treatment Group compared to the Control Group (2 [10%] versus 1 [5%], $p = 1.0$) for both drug classes. None of the patients were initiated on angiotensin receptor blockers or calcium channel blockers in this study group at the time of admission to hospital.

Biochemical Markers of Ischemia and Inflammation of the Cohort

In the analysis of the laboratory results measuring ischemia no statistically significant differences were found between the Treatment and Control Groups (Table 5). One creatine kinase level was missing in the data collected. For the remaining 39 patients the level of creatine kinase ranged from 31 U/L to 14 674 U/L with a mean (± SD) of 720.15 ± 1390.46 U/L in the Treatment Group compared to 1091.42 ± 3365.89 U/L in the Control Group ($p = 0.652$).

In May of 2003, the Dynakasper Medical Laboratories changed the diagnostic assay of myocardial infarction from Creatine kinase-myocardial cell isoenzyme (CK-MB) to Troponin I. Consequently, thirty CK-MB results were missing; and only during the first few months of randomization were values of both markers available. The mean (± SD) CK-MB was 9.67 ± 7.51 U/L in the Treatment Group compared

Table 4

Medications Initiated at the Time of Hospital Admission of the Study Cohort

Medication Classes (n [%])	**Treatment Group (n = 20)**	**Control Group (n = 20)**	**p value**
ASA	10 (50)	11 (55)	1.0
Heparin	12 (60)	11 (55)	1.0
Low Molecular Weight Heparin	6 (30)	8 (40)	0.741
β-Blocker	5 (25)	9 (45)	0.320
Angiotensin Converting Enzyme Inhibitor	7 (35)	7 (35)	1.0
Angiotensin Receptor Blocker	–	–	–
Calcium Channel Blocker	–	–	–
Diuretic	2 (10)	1 (5)	1.0
Thrombolytic	2 (10)	1 (5)	1.0
Glycoprotein IIb/IIIa	1 (5)	1 (5)	1.0
Thienopyridine	6 (30)	7 (35)	1.0
Lipid Lowering	5 (25)	5 (25)	1.0
Other	1 (5)	1 (5)	1.0

to 141.43 ± 334.78 U/L in the Control Group (p = 0.529), with a range from 2 U/L to 900 U/L. Troponin I has become the diagnostic marker of myocardial infarction at a level greater 1.5 μg/L. The laboratory where the blood samples are processed chose an upper limit of 50.0 μg/L for a diagnostic Troponin I. In this cohort, the mean Troponin I (± SD) was 4.16 ± 11.01 μg/L in the Treatment Group compared to 7.18 ± 13.72 μg/L in the Control Group (p = 0.448), with a range from below 0.15 μg/L to 50.0 μg/L.

To measure the degree of inflammation, C-reactive protein was assayed to determine if it could be used as a predictive measure for the incidence of CIRD. The C-reactive protein ranged from 2.3 mg/L to 249 mg/L, with a mean (± SD) of 29.09 ± 53.68 mg/L in the Treatment Group compared to 16.75 ± 15.89 mg/L in the Control Group (p =

0.330). The C-reactive protein level of 249 mg/L did not occur in any of the three patients who developed CIRD.

Table 5

Biochemical Markers of Ischemia and Inflammation of the Study Cohort

Biochemical Markers (M ± SD)	**Treatment Group (n = 20)**	**Control Group (n = 20)**	**p value**
Creatine Kinase (U/L)	720.15 ± 1390.46	1091.42 ± 3365.89	0.652
CK-MB*(U/L) (n = 10)	9.67 ± 7.51	141.43 ± 334.78	0.529
Troponin I (μg/L)	4.16 ± 1.01	7.18 ± 13.72	0.448
C-Reactive Protein (mg/L)	29.09 ± 53.68	16.75 ± 15.89	0.330

* CK-MB = Creatine Kinase-myocardial cell isoenzyme.

Cardiac Catheterization Characteristics of the Cohort

The analysis of the cardiac catheterization data (Table 6) found no differences between the study groups. Elective cardiac catheterization was completed on 18 (90%) and 19 (95%) in the Treatment Group and in the Control Group, respectively. Urgent cardiac catheterization was undertaken in 2 (10%) in the Treatment Group and 1 (5%) in the Control Group. Urgent cardiac catheterization was completed in these three patients due to persistent pain, persistent electrocardiographic changes, and chest pain and decompensation.

Coronary angiography showed that 2 (10%) in the Control Group and none in the Treatment Group had angiographically normal coronary arteries; while 3 (15%) versus 2 (10%) had one vessel disease, 2 (10%) versus 3 (15%) had two vessel disease, and 10 (50%) versus 11 (55%) had three vessel disease, in the Treatment Group and in the Control Group, respectively. Only two patients in the Control Group had three vessel disease with left main stem involvement compared to one patient in the Treatment Group.

In the Treatment Group, one patient (5%) had one vessel disease with left main stem and two patients (10%) with two vessel disease with left main stem involvement. There were no complications during cardiac catheterization in either study group.

At the discretion of the catheterizing Cardiologist, not every patient (13 study patients in total) had a left ventricular assessment at the time of angiography done via a ventriculogram. Of those who did have a ventriculogram there were 15 (75%) in the Treatment Group and 12 (60%) in the Control Group. The mean (± SD) ejection fraction in the Treatment Group was 44.67 ± 15.41% compared to 46.67 ± 10.52% in the Control Group, with a range from 10% to 70%.

Nineteen patients (95%) in each group received the contrast agent iohexol, and one patient in the Treatment Group received the third generation iso-osmolality nonionic contrast agent, iodixanol. One patient who developed CIRD did not have this data recorded on the catheterization report and upon follow-up this information was unattainable. Consequently, the volume of contrast agent used was also only available for 39 study patients and ranged from 70 ml to 380 ml, with a mean (± SD) in the Treatment Group of 147.50 ± 74.75 ml compared to 133.68 ± 58.04 ml in the Control Group ($\underline{p} = 0.525$). In one study patient who developed CIRD based on a 44 μmol/L increase in serum creatinine, the volume of iohexol used was 200 ml. In the second study patient who developed CIRD based on a 25% increase in serum creatinine from baseline, 110 ml of iohexol was used. In the third study patient who developed CIRD, the type and amount of contrast agent given was not available. The study patient who received iodixanol did not develop CIRD.

Table 6

Cardiac Catheterization Characteristics of the Study Cohort

Characteristics	**Treatment Group (n = 20)**	**Control Group (n = 20)**	**p value**
Elective Angiography (n [%])	18 (90)	19 (95)	1.0
Urgent Angiography (n [%])	2 (10)	1 (5)	–
Complications (n [%])	–	–	–
Type of contrast (n [%])			
Iohexol	19 (95)	19 (95)	–
Iodixanol	1 (5)	–	–
Volume of contrast (ml, M ± SD)	147.50 ± 74.75	133.68 ± 58.04	0.525
Coronary Anatomy (n [%])			
Angiographically Normal	–	2 (10)	–
1-Vessel Disease	3 (15)	2 (10)	–
2-Vessel Disease	2 (10)	3 (15)	–
3-Vessel Disease	10 (50)	11 (55)	–
1-Vessel Disease + Left Main	1 (5)	–	–
2-Vessel Disease + Left Main	2 (10)	–	–
3-Vessel Disease + Left Main	1 (5)	2 (10)	–
Ejection Fraction (%, M ± SD)	44.67 ± 15.41	46.67 ± 10.52	0.705

Incidence of Contrast-Induced Renal Dysfunction in the Cohort

The definition of CIRD used in this study was an absolute increase in serum creatinine of 44 μmol/L within 48 hours of contrast media exposure, and/or a relative increase in serum creatinine of 25% above baseline within 48 hours of contrast media exposure. Based on both of these definitions, the incidence of CIRD in this cohort was three (7.5%), with two (10%) in the Control Group and one (5%) in the Treatment Group (Table 7). If the first definition of an absolute increase in serum creatinine was utilized, only the two (10%) patients in the Control Group were captured. By utilizing the relative increase in serum creatinine to define CIRD, all three patients were captured. The primary hypothesis of this study was that the administration of N-Acetylcysteine and intravenous hydration would lower the incidence of CIRD compared to those who received placebo and intravenous hydration in this cohort of patients. There was a trend noted for a lower incidence of CIRD in the Treatment Group compared to the Control Group. No patients who developed CIRD in this cohort required dialysis therapy, however electrolyte levels, urine output, and acid-base levels were not recorded as part of the data collection.

Table 7

Incidence of Contrast-Induced Renal Dysfunction in the Study Cohort

Biochemical Markers (n [%])	**Treatment Group (n = 20)**	**Control Group (n = 20)**
Incidence of CIRD* Based on Increase of 44 umol/L	–	2 (10)
Incidence of CIRD Based on 25% Increase in Creatinine	1 (5)	2 (10)
Incidence of CIRD Based on Both Definitions	–	2 (10)

* CIRD = Contrast-Induced Renal Dysfunction.

Biochemical Markers of Renal Function at Baseline, 24 Hours, and 48 Hours in the Cohort

The biochemical markers of renal function that were recorded were the serum creatinine, creatinine clearance, and blood urea nitrogen levels, as well as protein levels in the urine on enrolment into the study. The Cockcroft-Gault formula was used to calculate creatinine clearance based on ideal body weight and serum creatinine (Table 8). The biochemical markers of renal function are graphically presented in Figures 3 and 4. There were three patients who were discharged on the day following coronary angiography. Laboratory requisitions were given to these patients with instructions to visit a laboratory the following day to have 48-hour blood samples drawn. A phone call was also made to remind them of the bloodwork which needed to be done for the study, but despite these efforts, these patients were lost to follow-up. Consequently, three serum creatinine and blood urea nitrogen levels at 48 hours were not available and the calculated creatinine clearance and interval changes were not completed. Thus there were two (10%) patients lost to follow-up in the Control Group and one (5%) in the Treatment Group.

Table 8

Biochemical Markers of Renal Function Over 48 Hours of the Study Cohort

Biochemical Markers (*M* ± SD)	**Treatment Group (*n* = 20)**	**Control Group (*n* = 20)**	**p value**
Serum Creatinine - baseline (μmol/L)	131.70 ± 41.57	127.32 ± 39.43	0.738
Serum Creatinine - 24hours (μmol/L)	127.95 ± 42.19	127.53 ± 36.25	0.973
Serum Creatinine - 48hours (μmol/L)	141.95 ± 49.52	139.47 ± 45.17	0.877
CrCl* - baseline (ml/min)	34.45 ± 10.55	35.84 ± 12.00	0.702
CrCl - 24 hours (ml/min)	35.50 ± 10.31	35.42 ± 11.38	0.982
CrCl - 48 hours (ml/min)	32.79 ± 11.06	33.06 ± 11.49	0.943
BUN - baseline (mmol/L)	10.93 ± 4.93	11.32 ± 5.63	0.820
BUN - 24 hours (mmol/L)	9.72 ± 5.06	10.36 ± 5.11	0.709
BUN - 48 hours (mmol/L)	10.31 ± 5.46	10.57 ± 5.27	0.883

* CrCl = Creatinine Clearance.

** BUN = Blood Urea Nitrogen.

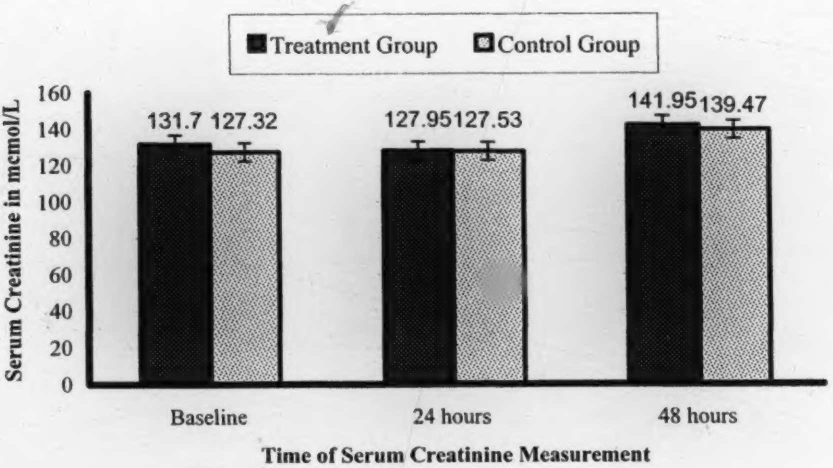


Figure 3. Mean Serum Creatinine During the Study Period

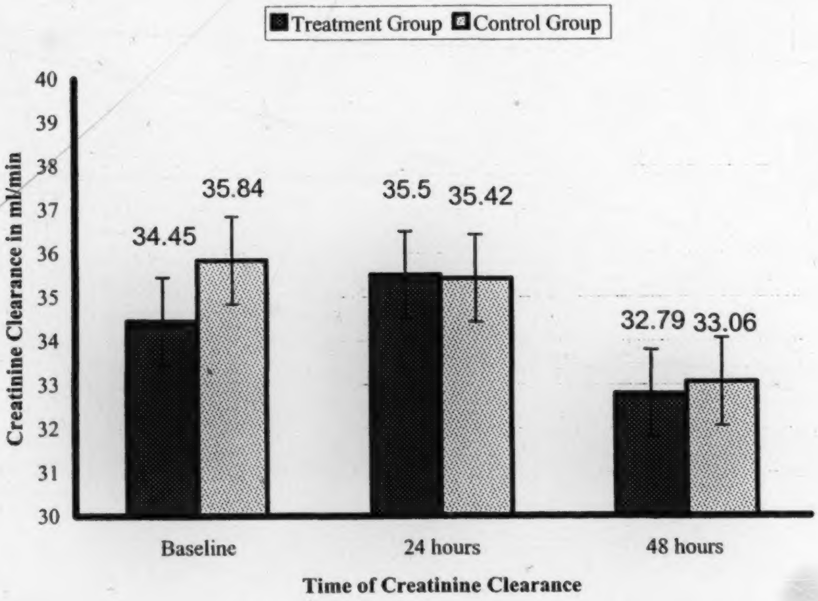


Figure 4. Mean Creatinine Clearance During the Study Period

The second hypothesis tested in this study was that there would be an attenuation in change in serum creatinine in patients who received N-Acetylcysteine and intravenous hydration compared to those receiving placebo and intravenous hydration in this cohort of patients. To test this hypothesis a repeated measures ANOVA was conducted on the serum creatinine from enrolment, to baseline, to 24 hours, and to 48 hours (Table 9). There was a statistically significant difference in serum creatinine over time (F = 5.555; df = 3; p = 0.001), specifically from 24 hours to 48 hours (F = 21.619; df = 1; p < 0.001) (Table 9). However, no significant differences were found between the Treatment Group and the Control Group (F = 0.09; df = 1; p = 0.925).

Based on the data available for t-test analysis, the mean (± SD) baseline serum creatinine was 131.70 ± 41.57 µmol/L in the Treatment Group and 127.32 ± 39.43 µmol/L in the Control Group (p = 0.738). The baseline serum creatinine of the cohort ranged from 74 µmol/L to 242 µmol/L the morning of coronary angiography. At 24 hours the range of serum creatinine was from 75 µmol/L to 228 µmol/L; with a mean (± SD) of 127.95 ± 42.19 µmol/L in the Treatment Group and 127.53 ± 36.25 µmol/L in the Control Group (p = 0.973). At 24 hours the Treatment Group had a small change towards improvement in serum creatinine (M ± SD = –3.75 ± 12.59 µmol/L), while in the Control Group there was no in change seen in the serum creatinine (M ± SD = 0.21 ± 8.60 µmol/L, p = 0.261). Serum creatinine ranged from 76 µmol/L to 267 µmol/L at 48 hours in the total cohort, with an increase in serum creatinine (M ± SD) from baseline to 141.95 ± 49.52 µmol/L in the Treatment Group and to 139.47 ± 45.17 µmol/L in the Control Group (p = 0.877). In the Treatment Group, the increase of change at 48 hours in the serum creatinine (M ± SD) was by 9.32 ± 11.20 µmol/L and in the Control Group was by 10.29 ± 18.93 µmol/L, (p = 0.850).

The third hypothesis tested in this study was the maintenance or improvement in creatinine clearance in patients who received N-Acetylcysteine and intravenous hydration compared to those receiving placebo and intravenous hydration in this cohort. To test this hypothesis a repeated measures ANOVA was conducted on the creatinine clearance from enrolment, to baseline, to 24 hours, and to 48 hours (Table 10). There was a statistically significant difference in creatinine clearance over time (F =5.246; df = 1; p = 0.002), again from 24 hours to 48 hours (F = 20.192; df = 1; p < 0.001) (Table 10) with no statistically significant differences found between the Treatment Group and the Control Group (F = 0.190; df = 1; p = 0.665)

The baseline creatinine clearance in this cohort ranged from 14 ml/min to 71 ml/min; with a mean (± SD) 34.45 ± 10.55 ml/min in the Treatment Group and 35.84 ± 12.00 ml/min in the Control Group (p = 0.702). At 24 hours the creatinine clearance (M ± SD) rose to 35.50 ± 10.31 ml/min in the Treatment Group and decreased to 35.42 ± 11.38 ml/min in the Control Group (p = 0.982). The Treatment Group saw a slight improvement in creatinine clearance (M ± SD) with a change of 1.05 ± 3.38 ml/min at 24 hours while the Control Group saw a negligible decrease by –0.42 ± 2.41 ml/min (p = 0.128). At 48 hours the creatinine clearance (M ± SD) decreased below baseline to 32.79 ± 11.06 ml/min in the Treatment Group and to 33.06 ± 11.49 ml/min in the Control Group (p = 0.943). At 48 hours the Treatment Group and Control Group both saw a decreasing change in creatinine clearance from baseline (M ± SD = –2.11 ± 2.96 ml/min and –2.53 ± 4.33 ml/min, p = 0.731) (Table 10).

Table 9

Levels and Change in Serum Creatinine From Enrolment Over 48 Hours in the Study Cohort

Serum Creatinine (μmol/L)	**Enrolment** (Level 1)	**Baseline** (Level 2)	**24 Hours** (Level 3)	**48 Hours** (Level 4)
Treatment Group (M ± SD)	139.05 ± 40.42	132.63 ± 42.49	130.16 ± 42.15	141.95 ± 49.52
Control Group (M ± SD)	139.50 ± 59.32	129.56 ± 39.58	129.89 ± 36.29	139.50 ± 43.83

	ANOVA Within Subjects				**ANOVA Between Subjects**			
	df	**MS**	**F value**	**p value**	**df**	**MS**	**F value**	**p value**
Level 1 Vs Level 2	1	2475.613	3.629	0.065	1	114.748	0.168	0.684
Level 2 Vs Level 3	1	42.344	0.403	0.530	1	72.831	0.693	0.411
Level 3 Vs Level 4	1	4233.267	21.619	0.000	1	43.862	0.224	0.639

Table 10

Levels and Change in Creatinine Clearance From Enrolment Over 48 Hours in the Study Cohort

Creatinine Clearance (ml/min)	**Enrolment** (Level 1)	**Baseline** (Level 2)	**24 Hours** (Level 3)	**48 Hours** (Level 4)
Treatment Group (M ± SD)	32.74 ± 8.59	34.89 ± 10.65	35.58 ± 10.59	32.79 ± 11.06
Control Group (M ± SD)	35.94 ± 14.00	36.44 ± 12.73	36.06 ± 12.26	34.00 ± 11.84

	ANOVA Within Subjects				**ANOVA Between Subjects**			
	df	**MS**	**F value**	**p value**	**df**	**MS**	**F value**	**p value**
Level 1 Vs Level 2	1	65.298	2.279	0.140	1	25.406	0.887	0.353
Level 2 Vs Level 3	1	0.806	0.104	0.749	1	10.644	1.378	0.248
Level 3 Vs Level 4	1	216.979	20.192	0.000	1	4.979	0.463	0.501

The blood urea nitrogen was also tracked over the study period of 48 hours, and all data were available except one baseline and three 24-hour blood urea nitrogen samples, in addition to those lost to follow-up. The changes to blood urea nitrogen were not an end point in this study, but were measured to determine a correlation to the incidence of CIRD, but because of the small sample size this was not completed (Table 8). The baseline blood urea nitrogen ranged from 4.5 mmol/L to 28.7 mmol/L with a mean (± SD) of 10.93 ± 4.93 mmol/L in the Treatment Group and 11.32 ± 5.63 mmol/L in the Control Group (*p* = 0.820). At 24 hours the blood urea nitrogen ranged from 3.9 mmol/L to 27.3 mmol/L with a mean (± SD) of 9.72 ± 5.06 mmol/L in the Treatment Group and 10.36 ± 5.11 mmol/L in the Control Group (*p* = 0.709). At 48 hours the blood urea nitrogen ranged from 4.3 mmol/L to 29.2 mmol/L with a mean (± SD) of 10.31 ± 5.46 mmol/L in the Treatment Group and 10.57 ± 5.27 mmol/L in the Control Group (*p* = 0.883).

Proteinuria was assessed prior to catheterization by a random urine for urinalysis in all except one study subject. Fifteen patients (75%) in the Treatment Group and 12 (60%) patients in the Control Group had no protein detected. One patient (5%) in the Control Group had 3+ protein, while 2 patients had 2+ protein and 3 patients had 1+ protein detected. In the Treatment Group, 3 (15%) patients and 1 (5%) patient had 1+ and 2+ protein, respectively, detected on urinalysis.

Effects of N-Acetylcysteine on Hospital Stay

To determine the impact of CIRD on length of hospital stay, the number of days in Cardiology was tracked (Table 11). The average length of stay (± SD) in Cardiology for the Treatment Group was 14.30 ± 8.47 days and was similar in the Control Group at 14.70 ± 12.29 days, (p = 0.905). The minimum length of stay was 3 day with the maximum being 51 days. The length of stay (M ± SD) following cardiac catheterization was also similar between both groups, with 7.15 ± 7.10 days in the Treatment Group and 8.45 ± 10.65 days in the Control Group (p = 0.652). The shortest stays were in those patients who were discharged the following day. There were nine patients who were discharged the day following coronary angiography in this cohort, with three in the Treatment Group and six in the Control Group. And the longest length of time in days following coronary angiography was 36 days, which was the same patient who spent 51 days in hospital before discharge.

Table 11

Length of Hospitalization of Study Cohort

Number of Days (M ± SD)	**Treatment Group (n = 20)**	**Control Group (n = 20)**	**p value**
Length of Stay in Cardiology	14.30 ± 8.47	14.70 ± 12.29	0.905
Length of following Catheterization	7.15 ± 7.10	8.45 ± 10.65	0.652

CHAPTER FIVE

Discussion

To determine the efficacy of N-Acetylcysteine in decreasing the incidence of contrast-induced renal dysfunction (CIRD), a prospective, double-blind, randomized, placebo, controlled study was conducted at the Royal Alexandra Hospital. Patients were enrolled with biochemical evidence of renal dysfunction admitted with an acute coronary syndrome with or without biochemical evidence of myocardial ischemia, who were scheduled for coronary angiography with or without concomitant percutaneous coronary intervention. Of 132 eligible patients, 40 patients consented and enrolled into the study. Each patient was assigned to one of two study groups by simple randomization done by the Pharmacy Department to receive either oral N-Acetylcysteine (Treatment Group) or placebo (Control Group) with intravenous hydration in both study groups.

This study cohort ($\underline{n}$ = 40) was made up of 65% males with a mean age of 75.55 years. The mean ($\pm$ SD) serum creatinine at the time of enrolment into the study was 135.95 $\pm$ 49.46 μmol/L with a creatinine clearance of 34.65 $\pm$ 11.31 ml/min. The Treatment and Control Groups were matched on admission diagnosis. Myocardial infarction accounted for 60% of the admission diagnoses, with 45% being non-ST elevation myocardial infarcts and 15% being ST elevation myocardial infarcts. The remaining 40% of patients were diagnosed with unstable angina, with 27.5% of them having high risk features on presentation. The amount of myocardial damage in those patients with myocardial infarctions was measured through serial creatine kinase levels and averaged 901.01 U/L. The Treatment and the Control Groups were also matched on the cardiac risk factors of body mass index, smoking status, hypertension, diabetes mellitus, known coronary artery disease, previous myocardial infarctions, dyslipidemia, and history of heart failure. The two groups were similar on medication profiles, both prior to admission and therapies that were initiated on admission to hospital, and cardiac catheterization characteristics (i.e., coronary anatomy and type and volume of contrast media administered). This cohort well represented the typical patient profile admitted to the Royal Alexandra Hospital with moderate renal dysfunction.

Incidence of Contrast-Induced Renal Dysfunction

The mean (± SD) baseline serum creatinine was 131.70 ± 41.57 μmol/L in the Treatment Group and 127.32 ± 39.43 μmol/L in the Control Group. When renal function was assessed at 24 hours following coronary angiography, there were minimal changes seen in the serum creatinine in both groups, with a mean (± SD) decrease in the Treatment Group of –3.75 ± 12.59 μmol/L and a negligible increase in the Control Group of 0.21 ± 8.60 μmol/L. However, at 48 hours the mean (± SD) serum creatinine rose by 9.32 ± 11.20 μmol/L in the Treatment Group and 10.29 ± 18.93 μmol/L in the Control Group from baseline. The changes seen in the serum creatinine in the first 24 hours are observations that have been demonstrated in other studies investigating N-Acetylcysteine (Tepel, Van der Giet, Schwarzfeld, Laufer, Liermann, & Zidek, 2000; Diaz-Sandoval, Kosowsky, & Losordo, 2002; Briguori et al., 2002; Shyn, Cheng, & Kuan, 2002; Adamian et al., 2002; Oldemeyer, Biddle, Wurdeman, Mooss, Cichowski, & Hilleman, 2003; Tadros et al. 2003; Kay et al., 2003; Baker, Wragg, Kumar, De Palma, Baker, & Knight, 2003).

There were two definitions used for CIRD in this study, with the first being an absolute increase of 44 μmol/L in serum creatinine within 48 hours and/or the second which was a relative increase by 25% above baseline serum creatinine. There were only two studies, one by Diaz-Sandoval et al. (2002) and the other by Briguori et al. (2002) that used two definitions for CIRD. Diaz-Sandoval et al. used both the absolute and relative increase in serum creatinine, whereas Briguori et al. used a relative increase in serum creatinine and the need for dialysis. The criteria for dialysis were not described. In a consensus report on CIRD, published in 1999, Morcos, Thomsen, Webb, and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology defined CIRD as "an impairment of renal function (an increase in serum creatinine by more than 25% or 44 µmol/L [occurring] within three days following the intravascular administration of a contrast medium in the absence of an alternative etiology" (p. 1611). It was based on this consensus report and Diaz-Sandoval et al. study that both of the definitions for CIRD were used in this study to aid in comparison of results with these studies.

The incidence of CIRD was 7.5% in this cohort, with 2.5% in the Treatment Group and 5.0% in the Control Group based on a relative increase in serum creatinine level from baseline of 25% or more. There were 5% of the patients who had an absolute increase in serum creatinine of 44 µmol/L, both patients were in the Control Group. No patients in this study required dialysis therapy. In reviewing the results of this study those patients who received N-Acetylcysteine did not gain any added protection than the group receiving hydration alone.

The dosing regimen of the study drug was similar to the dosing regimen used by Diaz-Sandoval et al. (2002) in the APART Trial. This trial showed an absolute risk reduction of 37% for CIRD in patients who underwent elective cardiac catheterization, which at the time of development of this study's protocol was the most promising data available in the use of N-Acetylcysteine. N-Acetylcysteine has been proposed to possess antioxidant properties and based on the pharmacokinetics of this drug the dosing used in Diaz-Sandoval et al. study seemed to have merit. In theory to give N-Acetylcysteine while there is contrast media circulating in the vascular system would donate the sulfhydryl groups to the glutathione metabolic pathway so that oxygen-derived radicals and vascular functioning would be improved. There were three patients who did not receive the final dose of N-Acetylcysteine, but none of those three patients developed CIRD. Similar to other studies with the exception of the study by Baker et al. (2003), which used higher doses of intravenous N-Acetylcysteine there were no adverse reactions to the ingestion of oral N-Acetylcysteine noted in this study. Baker et al. observed gastrointestinal side effects as the chief complaint.

In the three patients who developed CIRD, the age ranged from 67 years to 79 years, and two were male. The body mass index ranged from 24 kg/m^2 to 32 kg/m^2. One male was overweight and the second had a normal body mass index. The female patient who developed CIRD was obese. All three patients had more than four cardiac risk factors, which included known coronary artery disease, dyslipidemia, smoking, hypertension, two had diabetes mellitus, two had previous myocardial infarctions, and two had a history of congestive heart failure. Based on the medication profiles, two of the patients were taking potentially nephrotoxic agents prior to admission (i.e., lasix and aldactone).

Two of the patients who developed CIRD had an admission diagnosis of high risk unstable angina and one had a non-ST elevation myocardial infarction with a creatine kinase peak of 225 U/L and Troponin I of 0.93 µg/L. All three underwent elective coronary angiography and two of them received iohexol, 110 ml in one case and 200 ml in the second. In the third case this data was not recorded. All three had triple vessel disease, with the ejection fraction being 50% in two cases and 30% in one case. None of these patients underwent coronary intervention during their hospital admission. Because of the limited sample size and data on myocardial functioning it is difficult to determine if decreased forward blood flow could have been a potential mechanism for CIRD. Although two patients had an ejection fraction of 50%, there may have been a component of diastolic dysfunction, given that all three patients who developed CIRD had hypertension. Also given that patients had an acute coronary syndrome, there may have been some element of myocardial stunning or hibernation, which may have hindered myocardial functioning.

The C-reactive protein results were all greater than 3 mg/L in those who developed CIRD. This marker of inflammation was 40 mg/L in the male patient with the highest serum creatinine of 181 µmol/L and a creatinine clearance of 24 ml/min who also had 2+ proteinuria. The female patient who developed CIRD had a C-Reactive Protein of 4.3 mg/L with a serum creatinine of 115 µmol/L and a creatinine clearance of 33 ml/min; and in the third patient who was male the C-Reactive Protein was 4.6 mg/L with a serum creatinine of 146 µmol/L and a creatinine clearance of 36 ml/min. Both of the latter two patients had a negative urinalysis for microalbuminuria. The blood urea nitrogen ranged from 9.1 mmol/L to 24 mmol/L. Depending on the territory of myocardial ischemia and infarction seen in these patients and based on these blood urea nitrogen levels, it is difficult to determine if the level of hydration was adequate in these patients to ensure adequate filling pressures for an optimal cardiac output. Blood pressures were not recorded prior to coronary angiography or during the 48-hour study period.

Based on the literature, the incidence of CIRD is typically 10% to 40% in patients who undergo coronary angiography with evidence of renal dysfunction (Scanlon et al., 1999; Spinler & Goldfarb, 1992). One possible explanation for the lower incidence of CIRD at the Royal Alexandra Hospital can be attributed to the practices currently implemented for identified patients with renal dysfunction. The first is the use of other diagnostic imaging techniques (i.e., echocardiography, nuclear medical imaging, or exercise stress testing) to risk stratify patients with renal dysfunction. The second is the minimization of the volume of contrast media given to these patients. Typically, if a patient is identified with elevated serum creatinine levels or a decrease in creatinine clearance, ventriculograms are not preformed and coronary interventions are staged to allow 48 hours to 72 hours to pass so that the renal function may have a window of time to eliminate and recover from the initial contrast media exposure. As well, with the introduction of the low osmolality nonionic contrast media, iodixanol, Cardiologists have used this imaging media along with minimal volume to protect against CIRD in patients deemed to be at an increased risk.

Based on the use of two definitions of CIRD, the incidence was 7.5% in this study cohort. The question that needs to be answered is whether a relative or absolute increase in serum creatinine is the better indicator of renal dysfunction. It would stand to reason that absolute measurements of renal function are merely a guideline, but the assessment of the patient within his/her own context is a much better indicator of the level of dysfunction that is occurring secondary to the contrast exposure. The accurate measurement of renal function is through the measurement of the elimination of inulin. The measurement of serum creatinine is a surrogate idicator of renal function. The creatinine level of a patient is influenced primarily by three factors: (a) production, (b) volume of distribution, and (c) elimination. These three factors can be influenced by such things as body habitus, co-morbidities, and medication that impair renal tubular secretion of creatinine and those that chemically interefere with creatinine measurements. Ideally the glomerular filtration rate should be used to determine renal function and is better estimated using creatinine clearance, which takes into account both the serum and urine creatinine levels. The use of the Cockcroft-Gault formula provides an easy estimate of the glomerular filtration rate based on ideal body weight, age, and serum creatinine, but is only accurate if renal function is in steady state. The Cockcroft-Gault formula was used in this study because of the ease of calculation of creatinine clearance.

CIRD is an iatrogenic complication, which has increased in frequency due primarily because of the increase in use of coronary angiography and other contrast media investigations used for the diagnosis and risk stratification of patients. The cutting edge techniques in percutaneous coronary intervention are making angioplasty a more common management technique for patients with critical coronary artery lesions. Should the increase in serum creatinine, which is seen, be called dysfunction, insufficiency, impairment, failure, nephropathy, especially in the absence of electrolyte imbalances, oliguria, anuria, and acid-base disturbances, or a response? The renal system is responsible for the elimination of the foreign contrast media from the body. As the kidneys perform its function there is an elevation in serum creatinine. Perhaps the transient elevation in serum creatinine is merely reflecting functioning of the kidneys as it eliminates foreign material. The findings of Davidson et al. (1989) suggested that all patients have some measurable loss of renal function despite normal serum creatinine and creatinine clearance levels. In a retrospective study by McCullough, Wolyn, Rocher, Levin, & O'Neill (1997), it was found that the overall incidence of CIRD in 1826 consecutive patients was 14.5%, which was similar to the incidence found by previous investigators. However, only 7.7/1000 patients had an elevation in serum creatinine associated with an increase in potassium or a need for dialysis. In lieu of the data it seems reasonable to term CIRD more appropriately as contrast induced renal response.

The most common theory for CIRD is the profound vasoconstriction, which occurs secondary to the influence of contrast media on renal vasculature. There is also some evidence to suggest there is increased energy expenditure resulting from the tubular energy due to the osmotic stress of the contrast media (Erley, 2001). Whatever the mechanism the ischemia that results may actually cause necrosis or disruption in functioning of renal cells, which then leads to the transient or persistent elevation in serum creatinine that sometimes occurs.

Many studies have been published during the past several years to illuminate the high risk profile and increase in adverse outcomes of patients who develop CIRD following angiographic imaging (Bailey, 2001; Gruberg et al., 2000; Huber, Jeschke et al., 2002; McCullough, 2003; Mann et al., 2001; Marenzi, Marana et al., 2003; Nikolsky & Mehran, 2003; Vogt., et al., 2001). The pre-existing level of renal dysfunction, progressive age, diabetes mellitus, and the volume of contrast media given have been identified as predictors for the development of CIRD (AHA, 2001; Davidson et al., 1989; Deray & Jacobs, 1995; Morcos et al., 1999; Scanlon et al., 1999; Spinler & Goldfarb, 1992; Taliercio, McCallister, Holmes, Ilstrup, & Vlietstra, 1989; Tommaso, 1994). The co-morbidities identified as risk factors for CIRD suggest that patients with biochemical evidence of renal dysfunction that worsen with the exposure of contrast media may have a more advanced stage of cardiovascular disease. Thus the CIRD that is seen following coronary angiography, rather than being regarded as a complication of a diagnostic angiographic procedure, may be regarded as a prognostic marker of adverse outcomes.

Limitations of the Study

There were several limitations to this study that have been identified. The first is the study was a single-center trial. The sample size was projected to be 130 to power this study to 0.80 based on an absolute difference in the incidence of CIRD of 17%, and a two-tailed alpha of 0.05. The number of patients who were eligible and could be considered for enrolment may have been greater if there were several sites actively recruiting for patients. Consequently, subgroup analysis or regression analysis could not be completed as initially proposed to determine the independent risk factors for CIRD in this particular cohort, which included C-reactive protein. Each institution has a pattern for risk stratification of patients based on the availability of tests, which may vary from institution to institution. With a single-center trial the referral pattern for certain tests may influence the make-up of the cohort. The Royal Alexandra Hospital is a tertiary hospital with cardiac catheterization facilities. In addition to the patients who are admitted and those waiting for out-patient coronary angiography, the Royal Alexandra Hospital takes referrals from peripheral sites for the angiographic investigation of patients with an acute coronary syndrome. This referral process perhaps increases the number of this diagnostic investigation as a risk stratification method. The study only recruited patients who were admitted to the Royal Alexandra Hospital. This selection process made those patients who participated in the study a higher risk group who tended to have multiple co-morbidities.

The final limitation of this study was the lack of definition of clinically relevant CIRD. The monitoring of potassium, urine output, and other markers of impaired renal function would have provided more acute clinically relevant data into the significance of CIRD. As well, monitoring the serum creatinine at one month and at six months following coronary angiography would have provided a better indicator of any permanent renal dysfunction, which may have resulted from coronary angiography. The follow-up of the cohort six months to one year after enrolment would have provided insight into the morbidity and mortality associated with CIRD. Many papers have been published describing the association between mortality and the incidence of CIRD. In one such paper by Gruberg et al. (2000), which described the prognostic implications of CIRD in 439 patients, found that of those you required dialysis for CIRD the one year mortality was 45.2%, compared to 35.4% who did not require dialysis for CIRD, and compared to 19.4% for those who did not develop CIRD. These findings are similar to those found in a retrospective analysis of the Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease database of patients who underwent coronary angiography in Alberta from January, 1995 to December, 1997 (Hemmelgarn et al., 2001).

Implications of the Findings

From the results of this study and based on review of the current literature, several cohorts have been identified who require further large scale investigations into the use of N-Acetylcysteine to assess the efficacy of this drug in decreasing the incidence of CIRD.

The first is in patients undergoing coronary angiography who present with an acute coronary syndrome. This population makes a large proportion of patients undergoing angiography and with the added risk factor of stunned or hibernating myocardium there needs to be further investigations completed in evaluating the incidence of CIRD and benefit of N-Acetylcysteine in this cohort.

The studies by Tepel et al. (2000) and Shyu et al. (2002) show statistically that patients with severe renal dysfunction (a serum creatinine greater than 2.0 mg/dl) are the population who benefit the most from this therapy. A large-scale study that includes these cohorts of patients with moderate levels of renal dysfunction and those who receive larger volumes of contrast media may provide added evidence for the use of N-Acetylcysteine in a clearly higher risk group.

The inclusion of patients who are waiting as outpatients may provide evidence for the use of N-Acetylcysteine in a different patient population who are likely to be discharged the day following coronary angiography. The data generated would help determine the level and frequency of monitoring of renal function these patients require following angioplasty and stenting procedure and also further define what is clinically relevant CIRD.

As well, a study design to measure the long-term effects of contrast media on renal function should be developed. This would involve assessing the patient's renal function at one week, one month , six months, and one year after contrast media exposure. This data would then aid in assessing the long term risks and benefits of coronary angiography and perhaps utilizing less invasive strategies for high risk patients who present with an acute coronary syndrome and renal dysfunction.

The results of this study suggest that there was no added benefit gained in using N-Acetylcysteine compared to hydration alone in decreasing the incidence of CIRD. Based on these data and the data from the other studies which have been conducted in the use of N-Acetylcysteine a screening protocol may be developed and utilized for the appropriate review and introduction of hydration and N-Acetylcysteine therapy for those patients with renal dysfunction and an acute coronary syndrome. In addition to pre-existing renal dysfunction this protocol would include the major risk factors for CIRD, as well as the Quotient of Cigarroa (Huber, Jeschke et al. 2002) to determine the risk for CIRD and appropriately identify these patients so that prophylactic interventions may be implemented to decrease the incidence of CIRD.

Conclusion

The use of N-Acetylcysteine in acute coronary syndromes was conducted over a 10 month period in patients with biochemical evidence of renal dysfunction who underwent coronary angiography with or without concomitant percutaneous coronary intervention. The use of N-Acetylcysteine and intravenous hydration with 0.45% normal saline showed no added benefit in decreasing the incidence of CIRD compared to hydration alone in this patient cohort.

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Appendix A

INFORMATION SHEETS

The Efficacy of Oral N-Acetylcysteine and Intravenous Hydration Versus Placebo and Intravenous Hydration In Decreasing Contrast-Induced Renal Dysfunction In Patients Who Have Had an Acute Coronary Syndrome and Undergo Coronary Angiography With or Without Concomitant Percutaneous Coronary Intervention

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(780) 492-6795

Introduction:

You are being asked to participate in a study to evaluate the effectiveness of a medication, N-Acetylcysteine (Mucomyst, Parvolex) which may have in protecting your kidneys from the potentially harmful side effects incurred from the dye used for coronary angiography (a test to see the vessels that supply blood to your heart). Your physician has admitted you to the Royal Alexandra Hospital with a diagnosis of an acute coronary syndrome (heart muscle damage or risk of heart muscle damage); and your physician has determined the best method to investigate this damage is through the use of coronary angiography. The dye that is used for the coronary angiography can sometimes place a tremendous burden on the kidneys, especially if the kidney functioning is not optimal. The use of N-Acetylcysteine has been shown to have benefits in patients without a recent heart attack in protecting the kidneys from the potentially harmful side effects of the dye.

Procedure:

The purpose of this study is to compare the effectiveness of N-Acetylcysteine and fluids compared to fluids alone in protecting the kidneys from the potential harmful effects of the dye. N-Acetylcysteine has been used for approximately 50 years and has been used for different purposes, such as a remedy for Tylenol poisoning. The new use of this drug in protecting kidney functioning following dye exposure has been practiced in the hospital setting for about 2 years.

Requirements and Procedures:

You will receive the same medical care all patients with pre-existing renal function impairment.

If you agree to participate in this study, the following procedures will be done:

- ☐ As part of your standard hospital care a baseline medical history, physical examination, blood tests, and electrocardiograms (measurement of electrical activity of the heart muscle) will be preformed. You will be monitored closely during your hospitalization with blood collections, and urine output measurements as a standard part of your care. These measurements will monitor your kidney functioning as well as other important markers. If you are a woman of childbearing potential, a pregnancy blood test will be obtained to ensure that you are not pregnant. If your kidney functioning is found to be impaired daily measurements of your blood creatinine levels will be continued until the levels return to normal or the physician deems them stable.
- ☐ If the physician determines that you need a coronary angiography to investigate the heart muscle damage or the risk of heart muscle damage, you will be randomly (like flipping a coin) assigned to either receive the N-Acetylcysteine by mouth twice a day, one dose before and three doses following the coronary angiography, and fluids through an intravenous for six hours before the coronary angiography and for 12 hours after the coronary angiography; or a placebo (like a sugar-pill) by mouth twice a day, one dose before and three doses following the coronary angiography, and fluids through an intravenous for six hours before the coronary angiography and for 12 hours after the coronary angiography.
- ☐ You will be monitored after the coronary angiography for any complications or adverse effects. Blood tests will be taken 24 and 48 hours following coronary angiography to measure your kidney functioning and as deemed necessary based on your clinical condition.
- ☐ If your kidney functioning were to show signs of decreased functioning, continued monitoring and testing would be done until it returns to normal or is deemed to be stable by your physician as part of standard hospital care.

Potential Benefits:

There are no medical benefits that can be guaranteed to you for participating in this study. There is a chance that your kidney functioning may not be affected by the dye used in your coronary angiography. You may benefit from the knowledge that your participation in this study may guide the future treatment of patients with similar circumstances that require coronary angiography.

Risks:

There may be risks involved in your participation in this study. These risks include side effects (such as itchiness, hives, flushing, swelling of the face and lips, fast heart rate, asthma) due likely to the medication N-Acetylcysteine. These side effects are rare and have been seen with use of this medication in larger amounts than what is being used in this study. Although the medication that is being investigated has been used and studied for many years, there may be side effects that are currently unknown.

Confidentiality:

The personal information obtained about you during the course of this study will remain confidential. A number will be assigned to all data, which is collected or results which are recorded. Your data will be stored on a computer and backed up on a compact disk in compliance with applicable data protection laws.

Your consent to participate in this study also includes consent for your researcher to review all your medical records as may be necessary for purposes of the study. By signing the consent form you give permission to the study staff to access any personally identifiable health information, which is under the custody of other health care professionals as deemed necessary for the conduct of the research.

Voluntary Participation and Consent:

Your participation in this study is voluntary. You may refuse or you may withdraw from it at any time without penalty or loss of benefits to which you are otherwise entitled. If you terminate your participation, your researcher will promptly confer with you as to the best means of terminating your participation and arranging for your continued care.

Contact Persons:

You may contact Rajamalar Seyon at 780-491-5445 or Louise Jensen at 780-492-6795, if you have any study-related questions.

If you have any concerns and/or questions concerning your rights as a patient in an investigational study, you may contact: **Patient Concerns Office** at 780-407-1040.

Appendix B

CONSENT FORM

The Efficacy of Oral N-Acetylcysteine and Intravenous Hydration Versus Placebo and Intravenous Hydration In Decreasing Contrast-Induced Renal Dysfunction In Patients Who Have Had an Acute Coronary Syndrome and Undergo Coronary Angiography With or Without Concomitant Percutaneous Coronary Intervention

Investigator: Rajamalar Seyon, RN, MN (Candidate)
(780) 491-5445

Supervisor: Louise Jensen, RN, PhD
(780) 407-6795

Part 2 (to be completed by the research subject)	**YES**	**NO**
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your medical care?	☐	☐
Has the issue of confidentiality been explained to you, and do you understand who will have access to your records, including personally identifiable health information?	☐	☐
Do you want the investigator(s) to inform your family doctor that you are participating in this research study?	☐	☐

Who explained this study to you?______________________________________

I agree to take part in this study.

Signature of Research Participant   Date & Time

Printed Name

I, undersigned, have fully explained the relevant details of this study to the patient named above and/or to the person authorized to consent for the patient.

Signature of Researcher   Date & Time

Printed Name

Appendix C

ENROLLMENT CRITERIA

INCLUSION CRITERIA	YES	NO
1. Age ≥ 18 years	☐	☐
2. Scheduled for coronary angiography with or without concomitant PCI	☐	☐
3. Baseline creatinine of ≥ 125 μmol/L for males or 115 μmol/L for females; and/or creatinine clearance of < 50 ml/min	☐	☐
4. Diagnosed with an ACS with or without electrographic changes and/or quantitative biochemical markers as measured by CK, CK-MB, Ratio, and/or Troponin I	☐	☐
5. Able to provide informed consent and available for follow-up	☐	☐

EXCLUSION CRITERIA	YES	NO
1. Hemodynamic instability (systolic blood pressure < 90 mmHg) requiring inotropic support	☐	☐
2. Pregnant	☐	☐
3. Acute Gastrointestinal Disorder (Unable to tolerate po medication)	☐	☐
4. Killip class III or IV, NYHA III or IV, or patient deemed by the Cardiologist unsuitable to receive intravenous hydration therapy	☐	☐
5. Known sensitivity to N-Acetylcysteine (based on patient history or knowledge)	☐	☐
6. Current treatment with theophylline or mannitol	☐	☐
7. Dialysis therapy	☐	☐
8. Participation in another study or use of experimental drug	☐	☐

Appendix D

DATA COLLECTION TOOL

Hospital Number: **Study Number:**

Date of Admission: **Date of Discharge:**

Sex: M F **Date of Birth:** **Age:**

Height: **Weight:** **BMI:**

Medication Profile Prior to Admission:

Risk Factor Profile:

Smoker		Current	Never	Former
Hypertension (SBP>140mmHg DBP>90mmHg)		Yes	No	
Diabetes Mellitus	Type I Type II Insulin	PO H-glycemics	No	
Known CAD		Yes	No	
Previous MI		Yes	No	
Hypercholesteremia		Yes	No	
Family Hx of CAD		Yes	No	
CHF		Yes	No	

Diagnosis: NSTEMI STEMI Unstable Angina – High Risk Low-Risk

EKG on presentation: Territory:

Therapy Initiated on Admx:

ASA
Heparin
LMWH
β-Blocker
ACEI
Diuretic
Thrombolytic
IIbIIIa Inhibitor
Thienopyridine
Statin

Prior to Catheterization:

Killip: I II III IV

NYHA I II III IV

Catheterization: **Date:** # of days to cath from admission:

Elective

Urgent Reason: Decompensation Persistent EKG Changes Persistent Pain

Anatomy: 1VD 2VD 3VD and/or Left Main Ejection Fraction:

Culprit: TIMI: % Stenosis:

Contrast Media: **Type:** **Amount:** **(milliliters)**

Complications during Catheterization:

CIRD: **YES** **NO**

Other Complications?

Laboratory Flowsheet							
Date	CK	CK-MB	Troponin I	CRP	Creatinine	BUN	Creatinine Clearance
Initial Presentation							
Enrolment							
Morning of Cath							
24 hrs Post-Cath							
48 hrs Post-Cath							
hrs Post-Cath							
hrs Post-Cath							
hrs Post-Cath							
hrs Post-Cath							

Urinalysis	
Color/Turbidity	
Specific Gravity	
pH	
Protein	
Glucose	
Hemoglobin	
Leukocytes	
Ketones	
Microscopy	